

P/ NT COOPERATION TREAT

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

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Date of mailing (day/month/year) 30 May 2001 (30.05.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PE-3929	
International application No. PCT/BR00/00078	
International publication date (day/month/year) 25 January 2001 (25.01.01)	
International filing date (day/month/year) 14 July 2000 (14.07.00)	Priority date (day/month/year) 16 July 1999 (16.07.99)
Applicant INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
16 July 1999 (16.07.99)	PI 9902973-1	BR	NR
18 Febr 2000 (18.02.00)	PI 0003166-6	BR	22 May 2001 (22.05.01)

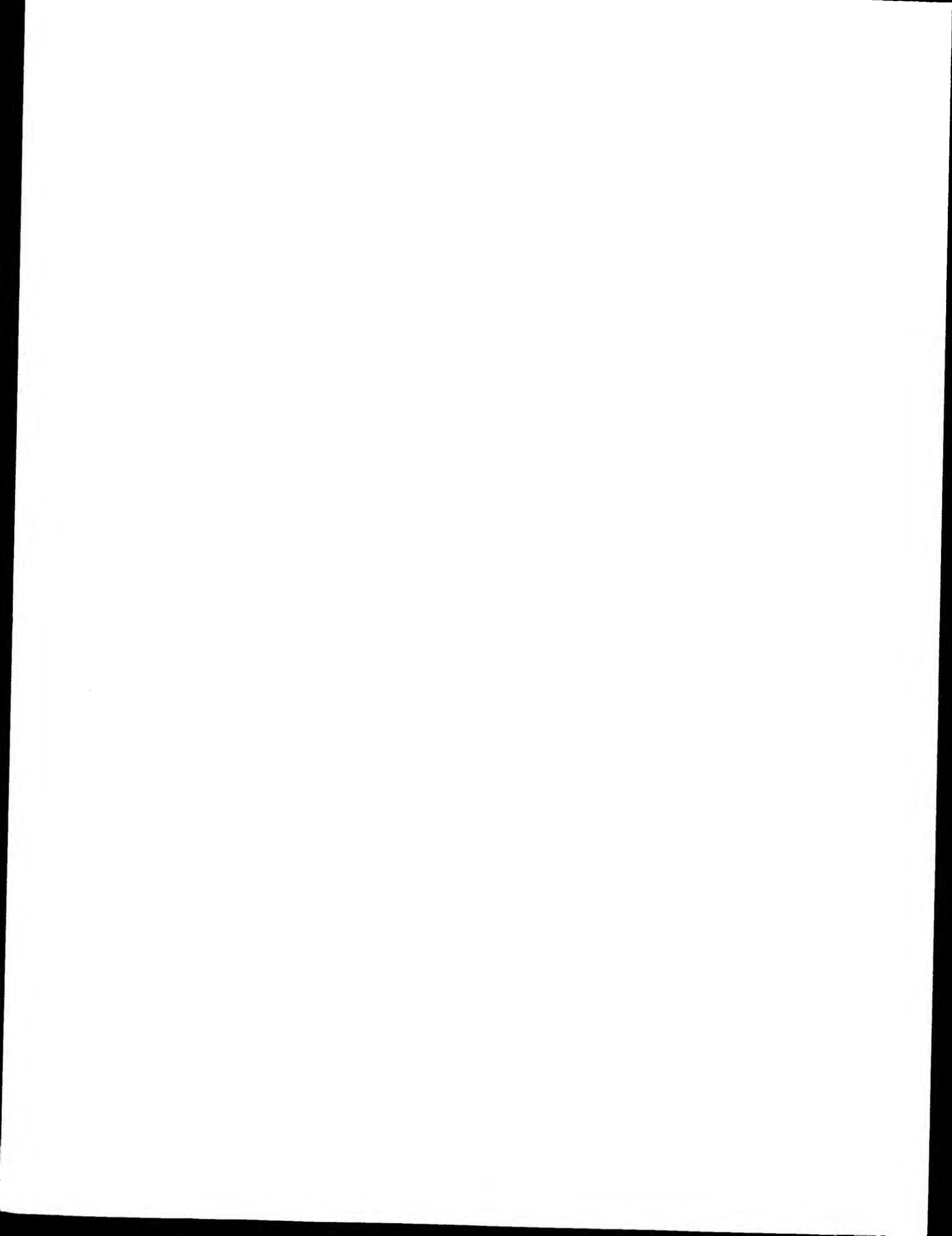
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Authorized officer

Marc Salzman

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TENT COOPERATION TRE. Y

PCT
NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
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United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
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Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 11 April 2001 (11.04.01)	Applicant's or agent's file reference PE-3929
International application No. PCT/BR00/00078	
International filing date (day/month/year) 14 July 2000 (14.07.00)	Priority date (day/month/year) 16 July 1999 (16.07.99)
Applicant ALCANTARA MARTINS ZUCCHETTI, Roberto et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
15 February 2001 (15.02.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Zakaria EL KHODARY
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Form PCT/IB/331 (July 1992)	

BR0000078

P ENT COOPERATION TREA

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

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Date of mailing (day/month/year)

11 October 2000 (11.10.00)

Applicant's or agent's file reference

PE-3929

IMPORTANT NOTIFICATION

International application No.

PCT/BR00/00078

International filing date (day/month/year)

14 July 2000 (14.07.00)

Applicant

INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA. et al

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. ☒ **Correction of priority claim.** In accordance with the applicant's notice received on: 15 September 2000 (15.09.00), the following priority claim has been corrected to read as follows:

BR 18 February 2000 (18.02.00) PI 0003166-6

- ☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

2. ☐ **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:

- ☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

3. ☐ As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:

4. ☐ **Priority claim considered not to have been made.**

- ☐ The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(1B).

5. ☒ In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):

BR 18 February 2000 (18.02.00) PI 0003166-6

6. A copy of this notification has been sent to the receiving Office and

- ☒ to the International Searching Authority (where the international search report has not yet been issued).
☒ the designated Offices (which have already been notified of the receipt of the record copy).

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003574963

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IS 95/11750A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 586 106 (JOHNSON & JOHNSON CONSUMER PRODUCTS) 9 March 1994 see page 4, line 50 - page 6, line 45; table 1	1-41,56
X	EP,A,0 440 398 (JOHNSON & JOHNSON CONSUMER PRODUCTS) 7 August 1991 see example 2	1-41,56
X	EP,A,0 343 444 (BAYER) 29 November 1989 see	1-41,56
X	EP,A,0 330 496 (BEECHAM GROUP) 30 August 1989 cited in the application see	1-41,56
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 February 1996

Date of mailing of the international search report

21.05.96

Name and mailing address of the ISA

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FISCHER, J

INTERNATIONAL SEARCH REPORT

International Application No

CI/US 95/11750

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO,A,95 25507 (PIERRE FABRE DERMO-COSMETIQUE) 28 September 1995 see the whole document</p> <p>-----</p>	1-41

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 11750

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. CLAIMS 1-41 AND 56
2. CLAIMS 42-54
3. CLAIM 55

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-41 AND 56

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

LACK OF UNITY OF INVENTION

No.	Searched	Subject
1	yes	Claims 1-41 and 56: A skin care composition
2	no	Claims 42-54: A two-compartment container
3	no	Claim 55: A method of storing a composition

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Rule 13.1 PCT deals with the requirement of unity of invention and states the principle that an international application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept. Rule 13.2 PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.

LACK OF UNITY OF INVENTION A PRIORI

The first problem underlying the present application consists of providing a skin care composition comprising certain specified retinoids stabilized against chemical (i.e. oxidative) degradation.

The proposed solution consists of incorporating those compounds into oil-in-water emulsions comprising a specific stabilizing system (claims 1-41 and 56). The special technical feature, defining the contribution which this invention, considered as a whole, makes over the prior art is to be seen in the specific stabilizing system.

The subject matter of claims 42-54 (a two-compartment container) may be used in relation to the skin care composition of claims 1-41 and 56.

This container, however is not effectively specifically designed for containing the skin care composition of claims 1-41 and 56. As a container it can be employed in a variety of uses, including pharmaceutical uses, and other uses which are not restricted to skin care compositions. Moreover, the components of the composition referred to in claims 42-52 and 54 are not restricted to the retinoids specified in claim 1, but may include any retinoid.

As such the subject matter of claims 42-54 lacks a common special technical feature with the subject matter of claims 1-41 and 56.

The second problem underlying the present application is to be seen in the provision of a two-compartment container in which its contents are out of contact with oxygen. The solution to this second problem is the provision of the container defined in claims 42-54. The special technical feature, defining the contribution which this invention, considered as a whole, makes over the prior art is to be seen in the particular features of the container. There is no technical relationship in the above sense with the first

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

mentioned problem and its solution.

The subject matter of claim 55 (a method of storing a composition in a two-compartment container) may be used in relation to the skin care composition of claims 1-41 and 56, and in relation to the subject matter of claims 42-54.

This method, however is not effectively specifically designed for storing the skin-care composition defined in claims 1-41 and 56. As a method it can be employed for storing a variety of compositions (including pharmaceutical compositions) in a variety of two-compartment containers (regardless whether contact with oxygen is to be avoided or not). Moreover, the skin care composition referred to in claim 55 is not restricted to the skin care composition specified in claim 1, but may include any skin care composition.

As such the subject matter of claim 55 lacks a common special technical feature with the subject matter of claims 1-41 and 56, and 42-54, respectively.

There is no technical relationship in the above sense with the first and second mentioned problems and their solutions. The problem underlying the subject matter of claim 55 must be defined as to provide a method of storing a composition in a two-compartment container. The special technical feature, defining the contribution which this invention, considered as a whole, makes over the prior art is to be seen in the particular features of the method.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed in the communication pursuant to Article 17(3)(a) PCT. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Searching these different subjects would have caused major additional searching efforts.

Only the first subject was searched.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

P S 95/11750

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0586106	09-03-94	AU-B- 4444893	10-02-94
		BR-A- 9303269	08-03-94
		CA-A- 2101101	07-02-94
		GR-A- 93100292	29-04-94
		JP-A- 7291847	07-11-95

EP-A-0440398	07-08-91	AU-B- 639063	15-07-93
		AU-B- 6997291	01-08-91
		CA-A- 2035086	30-07-91
		DE-D- 69100848	10-02-94
		DE-T- 69100848	11-05-94
		ES-T- 2048557	16-03-94
		HK-A- 94994	16-09-94
		JP-A- 4210902	03-08-92
		SG-A- 77794	14-10-94

EP-A-0343444	29-11-89	DE-A- 3817623	30-11-89

EP-A-0330496	30-08-89	AU-B- 3072989	31-08-89
		DE-D- 68909970	25-11-93
		DE-T- 68909970	10-02-94
		ES-T- 2059721	16-11-94
		JP-A- 2059518	28-02-90

WO-A-9525507	28-09-95	FR-A- 2717686	29-09-95
		AU-B- 2140895	09-10-95



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107/030985
Rec'd PCT/PTO 16 JAN 2002

Code: 311878002311878002

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Att.: M. Pregetter

International Preliminary

Examining Authority

VIA FACSIMILE
ORIGINAL BY MAIL

Fax.: 0049 89 2399 4465

Rio, September 14, 2001

Ref.: PCT - International Application PCT/BR00/00078
filed on 14.07.2000
INDUSTRIA E COMERCIO DE COSMÉTICOS NATURA LTDA.
Our ref.: PE-3929 (MCB)

Dear Sirs,

In response to the first written opinion issued on the above case, the applicant firstly presents new pages of the specification, a new set of claims and a new abstract in order to correct the irregularities mentioned by the examiner. The amendments and modifications are as follows:

- the quantitative values represented by decimal fractions have been corrected throughout the specification and claims;
- the definition of Dequest 2010 ® has been corrected to "1- hidroxyethylidene (1,1 diphosphonic) acid throughout the specification and claims;
- the term "disulfite" has been corrected to "bisulfite" (page 5, line 19, of the specification);
- the dependency relationship of claims 4, 20, 23 and 25 were reformulated;
- the term "reaction oxidation reverting compound" was redrafted as "reducing agent". As far as the expressions "deoxygenating compound" or "oxygen removing compound" are concerned, it is observed that the definition thereof is set forth on the passage bridging pages 3 and 4 of the originally filed specification and refers to "any compound or mixture of compounds able to diminish the oxygen solubility in a medium containing water and the antioxidant to be stabilized". This definition meets with the one specifically mentioned in the written opinion and, consequently, no modification was carried out thereon.

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f) Claim 15 has been has been modified to define that, in the particular embodiment mentioned therein, the antioxidant added in the second stage is an OPC and in that the first step also comprises the addition of LAA. This modification is supported by the original specification, page 5 (last line) to page 6, line 8.

Applicant respectfully submits that the above amendments are fully supported on the application as originally filed and do not represent addition of new matter.

Apart from the above amendments, applicants also submits some clarifications on the following points raised in the written opinion:

- i) the expression "two-phase" as used in the present application is meant to define a biphasic composition comprising a first phase containing the antioxidant, an oxygen-removing compound, a metallic ion sequestering agent and a reducing agent and a second comprising the hydrating compound;
- ii) although propylene glycol is a compound chemically similar to glicerín, for former can only be used for the purpose of the claimed process and composition as an oxygen removing compound. Although belonging to the group of glycols, the hydrating capability of propylene glycol is much lower than glicerín and in the quantitative range used it would never provide a hydrating effect.

According to the Written Opinion, the present claims are objected as not being novel when compared with documents D1, D2 and D3. Applicant, however, respectfully observe that none of the mentioned prior art references discloses a composition as claimed in the present application.

Firstly it should be noticed that the present claim 1 refers to process for wherein the antioxidant to be stabilized is mixed with specific compounds in an aqueous medium. The invention also refer to the resulting compositions comprising aqueous phases containing that antioxidant and some particular compounds. Thus, the present application does not aim to claim any composition comprising antioxidants and other compounds since this kind of composition would indeed be already known from the prior art. The new feature of the claimed composition is the fact that the antioxidant is present in the aqueous phase together with specific compounds.

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None of the mentioned prior art references discloses a process in which the ingredients are mixed in an aqueous phase in the way it is defined and claimed in the present application. It is, therefore, concluded that the present claims meet the criteria of novelty over the mentioned prior art.

Apart from the above, it should also be noticed that the composition as described in D1 must comprise a considerable number of chemical compounds to achieve the desired results. In addition, that prior art document does not mention which phase must comprise the respective ingredients and what would be results of including a ingredient in that particular phase. The composition of the present invention, on the other hand, overcome the prior art technical problems and makes it possible to reduce the number of necessary ingredients while achieve improved stability and cosmetic results.

D2 discloses compositions containing some components analogous to those used in the present composition. But again it is stressed that the new feature of the invention claimed in the present application is directed to the presence of the antioxidant together with an oxygen-removing compound, a metallic ion sequestering agent and a reducing agent in an aqueous medium, which aqueous medium will be used in the resulting cosmetic compositions. Moreover, D2 (page 31, line 25 to 29) mentions the drawbacks derived from the instability of Vitamin C which leads to the conclusion that those inventors did not develop a stabilized composition.

In fact, the compositions disclosed in D1 and D2 use derivatives of Vitamin C, namely a chemically modified derivative which is already stabilized (magnesium ascorbyl phosphate) and there is no mention that Vitamin C in its molecular form could be used without facing problems with its instability. Thus, neither D1 nor D2 mention nor foresee a composition in which Vitamin C (LAA) could be used in a stabilized form, as in the present invention.

D3 refers to stable emulsions containing ascorbic acid. However, such compositions necessarily comprise an organoclay material. Therefore, the technical effect obtained in accordance with those inventors is to produce a composition where the ascorbic acid is present in a liquid medium provided that a organoclay (e.g, bentonite) is added thereto. That document shows that bentonite surface is treated with ammonium chloride compound (claim 9). Such a modified composition has a positive charge in the presence of water while ascorbic acid would have a negative charge. It

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would provide an ionic or electrokinetic interaction between those two components.

The teachings of that prior art document does not anticipate the process and compositions as present claimed which do not involve the addition of a clay. In addition, D3 would never lead someone skilled in the art to attempt the stabiliation of antioxidants in a aqueous medium without any addition of clay or similar material.

In view of the clarifications presented above, the applicant respectfully submits that the invention as now claimed is novel and inventive over the prior art represented by D1, D2 and D3.

Very truly yours

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PCT

REC'D 23 OCT 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PE-3929	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/BR00/00078	International filing date (day/month/year) 14/07/2000	Priority date (day/month/year) 16/07/1999
International Patent Classification (IPC) or national classification and IPC A61K7/48		
Applicant INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.		


1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 18 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 15/02/2001	Date of completion of this report 19.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pregetter, M Telephone No. +49 89 2399 8719





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BR00/00078

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-12 as received on 14/09/2001 with letter of 14/09/2001

Claims, No.:

1-45 as received on 14/09/2001 with letter of 14/09/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BR00/00078

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-45
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-45
Industrial applicability (IA)	Yes:	Claims 1-45
	No:	Claims

2. Citations and explanations -
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US-A-5 804 168 (MURAD HOWARD) 8 September 1998 (1998-09-08)

D2: WO 99 33439 A (ROBERTS RICHARD L ;GREENE JAMES A (US);
SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08)

D3: US-A-5 902 591 (HERSTEIN MORRIS) 11 May 1999 (1999-05-11)

2. The subject-matter of present claim 1 is not novel according to Article 33(2) PCT. A process of contacting several compounds in aqueous medium necessarily takes place, when said compounds are all contained in the same aqueous solution/dispersion. Consequently, the same argumentation as given under point 3 applies.
3. The subject-matter of present claim 16 is not novel according to Article 33(2) PCT. D2 describes an oil-in-water formulation comprising an antioxidant compound in the aqueous phase (magnesium ascorbyl phosphate), a deoxygenating compound/oxygen removing compound (the most common humectants are glycols, which are given as examples of deoxygenating compounds), a metallic ions sequestering agent, a reducing agent (superoxide dismutase), and, in the dispersed phase, immunomodulator (beta glucan) and moisturizers/emollients (e.g. example 6). D3 discloses a mixture of 5% powdered ascorbic acid with 95% of an emulsion resulting in dissolving the ascorbic acid in the aqueous phase of said emulsion. The resulting aqueous phase comprises the ascorbic acid (antioxidant), a deoxygenating agent (butylene glycol), a metallic ions sequestering compound (EDTA) and a reducing agent (superoxide dismutase).
4. The subject-matter of present claim 28 is not novel according to Article 33(2) PCT. D2 describes an oil-in-water formulation comprising an antioxidant compound in the aqueous phase (magnesium ascorbyl phosphate), a deoxygenating compound (the most common humectants are glycols), a metallic ions



sequestering agent and a reducing agent (superoxide dismutase), and, in the dispersed phase moisturizers/emollients (hydrating comp.). Proanthocyanidins in the form of grape seed extract are also present (e.g. example 6).

5. With regard to the dependent claims, it is noted that a positive opinion can only be given, if dependent claims refer to independent claims that meet the requirements of the PCT.

Furthermore, the following has to be noted:

The use of a substance in certain percentages can only be considered to involve an inventive step, if it can be clearly shown that said percentages are unusual in the art and lead to a surprising effect.

The use of a specific immunomodulator, reducing agent, sequestering agent, ... can only be considered to involve an inventive step, if such a use is unusual in the art and leads to a surprising effect. However, the combination of specific compounds in specific percentages is very often not suggested by the prior art.

Re Item VIII

Certain observations on the international application

1. The subject-matter of claims 1, 16 and 28 is defined by using the term "comprise". This term "comprise" does not exclude the presence of further compounds.
2. Claim 38 defines glycerin as the hydration compound. The compound agent, according to claim 28 is in the "second phase". It is not clear, why glycerin should be present in the "second phase" and remain there, when chemically similar compounds, such as propylene glycol, are in the "first phase" (aqueous).

(19) World Intellectual Property Organization
International Bureau



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(25) Filing Language: English

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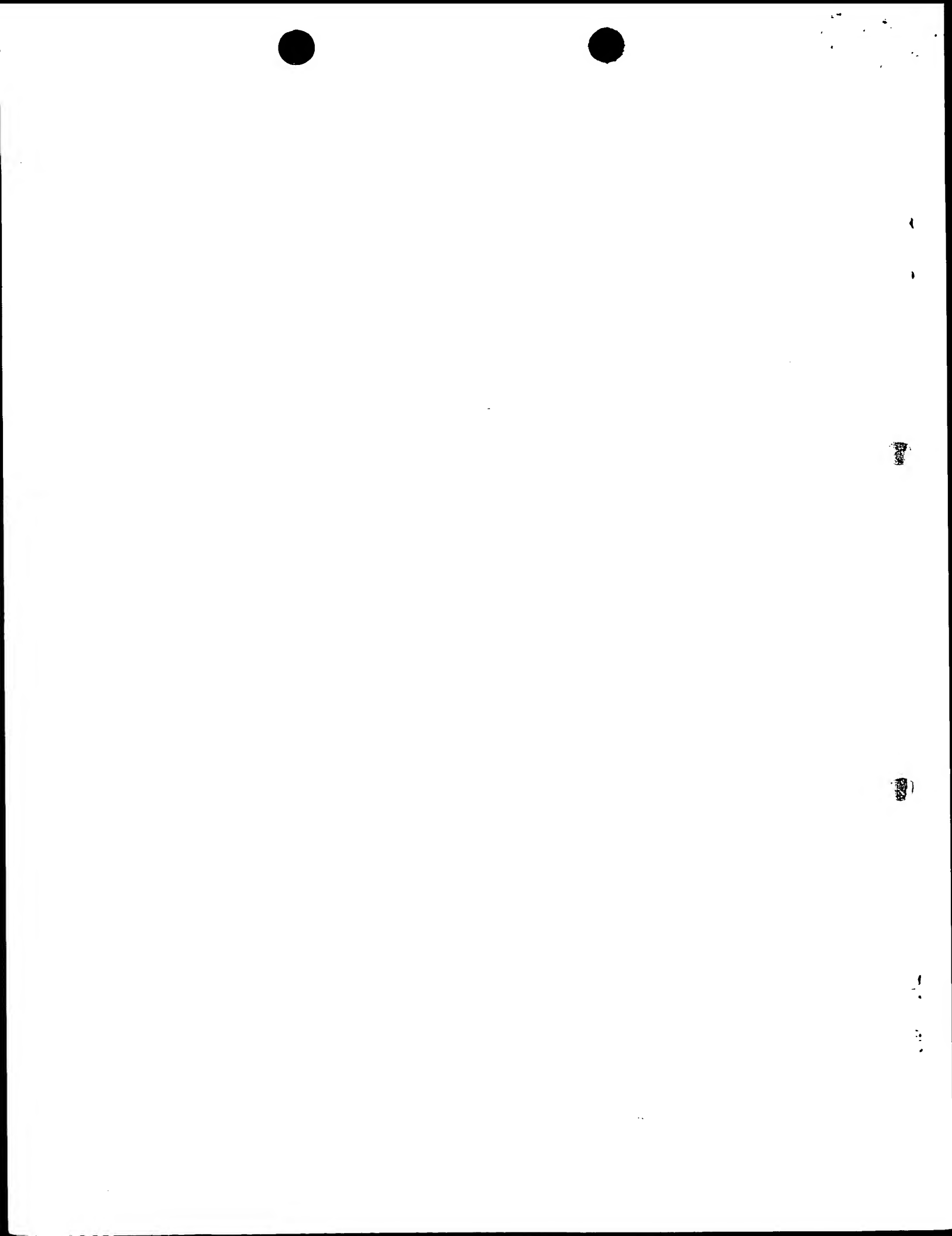
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A PROCESS FOR STABILIZING ANTIOXIDANT COMPOUNDS, AND AQUEOUS COMPOSITIONS

(57) Abstract: The present invention is directed to a process for stabilizing antioxidant compounds comprising the step of adding to said compound, in an aqueous mean, at least an oxygen-removing compound, at least a metallic ion sequestering compound and at least an oxidation reaction reversing compound. The invention is particularly useful to stabilize antioxidant compounds such as levogyrous ascorbic acid (LAA), popularly known as "Vitamin C", and the LAA associated with proantocyanidines (OPC) for the preparation of pharmaceutical and cosmetic compositions.



WO 01/05367 A1



**Title: "A PROCESS FOR STABILIZING ANTIOXIDANT COMPOUNDS, AND
AQUEOUS COMPOSITIONS"**

Field of the Invention

5 The present invention relates to an improved process for stabilizing antioxidant compounds useful in cosmetic and pharmaceutical compositions.

Background of the Invention

10 An antioxidant compound is any compound or mixture of compounds that, when in contact with the skin, is capable of protect the skin against the action of free radicals.

15 Antioxidant compounds such as levogyrous ascorbic acid (LAA), popularly known as "Vitamin C", and proantocianidines (OPC) are widely used in the pharmaceutical and cosmetic industry since, among other characteristics, they act against the free radicals that speed up the aging process and degeneration of the cells.

20 One of the greatest technical difficulties for the use of the above antioxidant compounds is their instability. The LAA, for example, can easily be oxidized in the presence of atmospheric air, metallic ions or water, thus being transformed into dehydroascorbic acid, in addition to other by-products resulting from the oxidation. Such transformation diminishes its physiological properties, mainly under use conditions where the compound is exposed to the atmospheric air, metallic ions and water such as, for example, when incorporated into a topic solution.

25 In a simplified way, the instability of an antioxidant is expressed as a decrease of its reducing ability before it is contacted with the skin. In the case of the LAA, its instability is expressed as a compound degradation reaction.

 In the case of the OPC's the instability occurs through an oligomerization reaction, followed by polymerization.

30 The LAA is often used in the form of its salts or esters due to this instability. The compositions prepared in this way attain stability for long periods of time.

Many studies have been carried out in order to obtain an aqueous composition containing stable antioxidant compounds. Some alternatives to stabilize LAA are described in Brazilian Patent Applications PI 9704418-0 and PI 9704728-7, filed by the same applicant of the present application. In said patent applications, processes for stabilizing levogyrous ascorbic acid (LAA) in a water-containing mean are disclosed comprising the step of contacting the LAA with at least one compound capable of forming hydrogen bridges with the LAA.

Another procedure known from the art for stabilizing antioxidants involves the association thereof with the compounds capable of reverting the decomposition reaction, the so-called "reverting compounds". Once again, considering the LAA, for example, said compounds revert the dehydroascorbic acid formation reaction. However, the stabilization through this process results in compositions unacceptable for cosmetic use and many times unsuitable for medicinal use, since the required stoichiometric amount of reverting compounds within the stoichiometry limits of the reaction must be too high so that the desired results could be attained. Since the reverting compounds usually are selected from sulfur-containing compounds, the high content thereof in the resultant compositions bring about an unpleasant odor and sometimes their use are even legally forbidden. For example, in a solution containing a concentration of 5% by weight of LAA, which is a concentration range generally used in cosmetic-pharmaceutical products, contents of approximately 20% by weight of reverting compound should be required to ensure the LAA stability.

Another prior art reference that can be cited and that teaches the use of reverting compounds, is a work published by Wrinkler, B.S. (Biochim, Biophy, Acta, 1117, 1992, pages 287 through 290), in which a compound is described (Glutathion) that can act as a reducer or reverting compound of dehydroascorbic acid by transforming same into ascorbic acid in the stoichiometric form. Through this work it was discovered that it was impossible to keep stoichiometric amounts of the components to produce a cosmetic composition since the Glutathion has an unpleasant odor which is a characteristic of sulphidric compounds.

Therefore, it is an object of the present invention to provide a process for stabilizing antioxidant compounds, that is, anti-free radicals or "anti-radicals", that

makes it possible to overcome the drawbacks common to the known processes, among which the ones that use the so-called reverting compounds and, in a special way, that can result in stable, cosmetically more pleasant and more efficient compositions, also suitable for pharmaceutical use.

5 **Summary of the Invention**

The present invention is directed to a process for stabilizing antioxidant compounds comprising the step of adding to said compound, in an aqueous medium, at least one oxygen-removing compound, at least one metallic ion sequestering compound and at least one oxidation reaction reverting compound.

10 The invention is also directed to compositions containing antioxidant compounds stabilized according to the above process.

Brief Description of the Drawings

Figure 1 shows a stability graph of compositions containing LAA according to formulas prepared in accordance with the invention during at least 90
15 days at room temperature.

Figure 2 shows the stability graph of compositions containing OPC that is an oligomer of grape seed, with which it is possible to measure the stability of said OPC.

Detailed Description of the Invention

20 The present inventors have now found out that the association of at least one antioxidant compound with an oxidation reaction reverting compound, in an aqueous medium, even without fulfilling the stoichiometry limits of the oxidation reaction, together with an oxygen-removing compound and a metallic ion sequestering agent, makes it possible to stabilize said antioxidant compound.

25 For the purposes of the present invention, some definitions of the terms used herein are given below.

An oxidation reaction reverting compound, or simply reverting compound, is to be understood as any compound or mixture of compounds having a higher oxidation potential than the oxidation potential of the oxidant to be stabilized
30 so that the concentration of antioxidant sub-compounds to be generated turns back to the original antioxidant in its molecular form.

As to the oxygen-removing compound, or simply oxygen remover, is any

compound or mixture of compounds capable of decreasing the oxygen solubility in a medium containing water and the antioxidant to be stabilized.

The metallic ion sequestering, or simply sequestering agent, is any compound or mixture of compounds having a high complexing constant and being effective for capturing and retaining such ions at pH values lower than 5.0. The effectiveness of the sequestering agent is defined by its ability to complexing the metallic ions present in a medium containing water and the antioxidant to be stabilized, so that it can minimize and preferably prevents the decomposition catalysis of any antioxidant present in said medium.

The invention is particularly suitable for providing the stabilization of compositions containing antioxidant compounds such as levogyrous ascorbic acid (LAA), or proantocianidines (OPC), or both, the resultant stability being effective for long periods of time.

In a first embodiment of the invention which is related to the stabilization of LAA in a aqueous medium, the oxygen-removing compound is selected from the group consisting of glycols, more preferably among propylene glycol and butylene glycol as well as mixtures thereof, even more preferably the propylene glycol.

The metallic ion sequestering compound, on its turn, is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates including di-, tri-, tetra- and pentavalent acids, the salts and mixtures thereof. More specifically the compound capable of sequestering metallic ions can be selected from the group consisting of sodium salt of 1-hydroxy ethylidene(1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra(methylenephosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta(methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate)acid, and mixtures thereof. Preferably, 1-hydroxy ethylidene(1,1-diphosphate) acid is used as the metallic ion sequestering agent, which is commercialized under the name Dequest 2010 supplied by MONSANTO.

In accordance with a preferred embodiment of the invention, the process for stabilizing antioxidant compounds comprises a first step wherein an aqueous solution containing the oxygen-removing compound and the metallic ion

sequestering agent at a ratio ranging from 2500:1 to 50:1 is prepared. In a second step, the antioxidant compound is then added to the resultant solution in a aqueous medium.

In a third step, a LAA oxidation reaction reverting compound is incorporated in the solution prepared in the first step described above, at a ratio ranging from 2520:1 to 20:1 related to the total mass of the oxygen-removing compound plus the sequestering agent mass, and at a ratio ranging from 1:0,02 to 3000:1, relating to the mass of the oxidizing compound. The great advantage achieved by the present invention is the notable stability of the LAA as time goes by. Compared to the compositions already known of the prior art containing this type of reverting compound, the invention allows the use of reverting compounds in significantly low amounts, thus making it possible to use same for cosmetic and/or pharmaceutical compositions, thus advantageously overcoming the aspect of unpleasant odor and the legal limitations concerning the concentration of reverting compounds.

Suitable oxidation reaction reverting compounds are those conventionally known for that purpose and include sulfur-containing compounds, preferably those selected from the group consisting of sodium dithionite, bissodium disulfites, calcium dissulfites, potassium bissulfites and still more preferably Glutathion, as well as mixtures thereof.

Usually, for obtaining a commercially suitable cosmetic composition containing, for example, LAA as the antioxidant agent, the latter is used in a range from about 0.01% to about 30% and preferably from about 0.5% to about 20%, by weight, while the oxygen-removing compound is used in a range from about 10% to about 25%, preferably from about 16% to about 19%, and the sequestering agent is used in a range from about 0.01% to about 0.20%, preferably from about 0.10% to about 0.20%, all the percentages being by weight, based on the total weight of the composition. The oxidation reverting compound is present at a concentration from about 0.01% to about 0.5%, preferably from about 0.05% to about 0.2%. However, the amounts of these components will depend on the end uses for the resultant composition and should not limit the scope of the invention.

Among the antioxidant compounds of high importance in the cosmetic

and pharmaceutical industry, the OPC's can also be cited, and they are advantageously stabilized by the process of the present invention. Regarding those OPC's that can be stabilized by the process of the invention, a more preferred embodiment of the process comprises a first step of preparing a first composition
5 comprising the oxygen-removing compound, the sequestering agent and the oxidation reverting compound, which is then added to the OPC contained in an aqueous medium. In this preferred embodiment, the first composition contains other antioxidant, preferably the LAA.

Although the reasons are not yet fully defined, it was noticed that the
10 presence of another antioxidant having characteristics similar to LAA in the first composition favors the stabilization of the OPC's. Without being too theoretical, it is believed that there is a synergy between the LAA present and the OPC's, resulting in an advantageously stable composition.

In a particularly advantageous way, an aqueous composition containing
15 the stabilized antioxidant in accordance with the present invention is used in a two-phase cosmetic composition. This kind of composition comprises, in a first phase, at least one antioxidant compound, an oxygen-removing compound, a metallic ion sequestering compound and an oxidation reaction reverting compound and, in a second phase, at least one hydrating compound. Preferably, the first and second
20 phases are used at a weight ratio between them from 12:8 to 20:11, preferably of 16:9.

The two-phase composition described above has proved to be particularly suitable for regions where the skin is more delicate and, consequently, where it requires special care. "More delicate skin" must be understood as the one
25 more sensitive to the use of formulations that contain antioxidant compounds, emulsifying systems, fragrances, preservatives, cosmetic agents, among others. In the case of some antioxidant compounds, the use of high concentrations and the nature of these compounds can cause a higher exfoliation and irritation to the user skin and a discomfort sensation.

30 For example, the delicate region around the eyes as well as other areas of the body require special care since the skin is thinner and fragile. The skin structure in this region is different: the epidermis and dermis are thinner, thus being

more susceptible to the external aggressions and facilitating to the appearance of wrinkles and expression marks. Collagen and elastin, that contribute to a higher skin stiffness and elasticity are also present in a lower amounts that helps to characterize the delicacy of the region.

5 Hydrating agents as herein defined and useful for the present invention are those compounds or mixtures of compounds capable of increasing the water retention and restructuring the skin barrier for preventing the loss of water.

10 In a preferred way to formulate said two-phase composition, its first phase comprises an aqueous composition comprising an amount of 0.2 10%, preferably from 0.5 and 2%, of acid ascorbic and about 0.001 to 2,2%, preferably from 0.01 to 1,0%, of OPC's, particularly OPC from grape seed, and in its second phase a mixture of hydrating agents such as glycerin present at a cocentration of 1.0 to 10% and 0.5 to 3,0% of ceramides contained in a liquid crystal emulsion, also called lamellar ceramide.

15 The lamellar ceramides help to restore the skin protection barrier, thus reinforcing the skin structure and consequently preventing the excessive loss of water. Together with glycerin, which is a soft hydrating agent and that increases the retention of water by the skin, it improves the hydration and softness thereof. The high glycerin concentration also provides a high hydration potential.

20 In as still more preferred way, the two-phase composition containing antioxidants stabilized in accordance with the invention is in the form of a homogeneous emulsion comprising an emulsifying system including at least two emulsifiers, one of which is selected from the group consisting of organosilicones of the copolyol family, preferably cetyl dimethicone copolyol, and a second one the
25 molecular structure of which is similar to the natural skin lipids, preferably selected from a lipophylic stearic acid derived from a polyglycerol, more preferably polyglycerol-4-isostearate. The emulsifying system is advantageously added at a concentration of 0.5 to 8% by weight, based on the total weight of the composition.

30 In this emulsion form, the antioxidants together with the emulsifying system form micro-particles the size of which provides the emulsion with a better effectiveness and homogeneity. Since they are protected in micro-particles, the antioxidants, especially when it is OPC of grape seed, act on the walls of the blood

vessels reinforcing same, what contributes to reduce the appearance of dark rings under the eyes and avoid the formation of such dark rings. Preferably, the emulsion particles are smaller than 3 μm , more preferably smaller than 2 μm , and still more preferably smaller than 1 μm .

5 The cosmetic composition as herein described may also comprise in its second phase from 13 to 25%, preferably from about 16 to 22% of emollients, from about 1 to 4% of an anti-radical agent, more preferably from 1.5 to 3,5% of Vitamin E, from about 0.001 to 0,3% of a preservative, more preferably 0.01 to 0,3% of sodium benzoate, and from about 0.05 to 0,6% of a thickening agent, more
10 preferably from about 0.15 to 0,4% of colloidal silicon dioxide.

 It was observed that the selection of the preservative agent is an important factor for the stabilization of the emulsion micro-particles due to its stripping ratio between the water and oil phases.

 The illustrative examples and tests given below will better describe the
15 present invention. However, the illustrated data and procedures merely refer to some embodiments of the present invention and should not be understood as limiting the scope of the invention.

Example 1

 Comparative tests carried out by the inventors confirm the important
20 paper of the reverting compound in the stabilization of antioxidants as per information obtained by Wrinkler B. S. in his work cited herein. A first test was carried out in order to determine the degradation kinetics of a 10% LAA solution in water-containing medium (m/v) under ultraviolet radiation, using a ultraviolet spectrophotometer, for 60 minutes. An immediate degradation of the LAA was
25 observed, wherein a concentration of molecular LAA of about 9,58% (m/v) remained.

 A stoichiometric amount of the reverting compound of the oxidation reaction, that is, Glutathion, was added to the previous post-irradiated solution. The resultant solution was irradiated with ultraviolet radiation for further 60 minutes. By analyzing the remaining LAA, it could be noticed that 9,50% (m/v) thereof was still
30 present. Therefore, the degradation of the LAA is dramatically minimized after the reverting compound is added.

 In a third test, a 10% LAA solution was prepared in a water-containing

medium (m/v) with a stoichiometric amount of the oxidation reaction reverting compound Glutathion. The solution was irradiated with ultraviolet radiation for 60 minutes. By analyzing the remaining LAA, a high content of 9.98% (m/v) was attained, thus confirming that the reverting compound inhibits the degradation of LAA. However, the use of said compound in stoichiometric amounts still presents the already mentioned disadvantages.

For the purpose of evaluating the invention, stability tests of the antioxidants LAA and LAA associated with OPC's in a water-containing medium have been carried out. Twelve different formulas were prepared in accordance with the invention, the chemical compositions of which as well as the obtained results are discussed in the following Tables I and II.

Table I

Formula	Glutathion (%) m/v) Reverting compound	OPC (%) m/v) Antioxidant	LAA (%) m/v) Antioxidant	Remaining LAA (%) m/v)
1	0.05	0	10	9.82
2	0.10	0	10	9.92
3	0.05	2	10	9.82
4	0.10	2	10	10.00

Table I shows the stability results of the LAA and OPC's measured by the respective remaining percentages, wherein formulas 1 through 4 have been prepared in accordance with the invention: formulas 1 and 2 including only LAA and formulas 3 and 4 comprising LAA associated with OPC's.

In the above tests, formulas 1 through 4 also comprise propylene glycol as an oxygen-removing compound, 2010 Dequest as the metallic ion sequestering agent and water.

It can be noticed from Table I that formulas 1 through 4 prepared in accordance with the invention show a LAA stability very close to 100% compared with the initial concentration.

Next, tests with further eight formulas have been carried out to evaluate

the stability of LAA plus a gelling agent (Modified Xanthane Gum). Formulas 5, 8, 11 and 12 include sodium dithionite as an oxidation reaction reverting compound, and formulas 6, 7, 9 and 10 use, again, Glutathion as the reverting compound, as shown in Table II

5

Table II

Formulas	Glutathion (% m/v) Reverting compound	Sodium dithionite (% m/v) Reverting compound	LAA (% m/v) Antioxidant	Remaining LAA (% m/v)
5	0.00	0.05	5.0	5.0
6	0.10	0.00	5.0	5.0
7	0.05	0.00	5.0	5.0
8	0.00	0.10	5.0	5.0
9	0.05	0.00	10.0	10.0
10	0.10	0.00	10.0	10.0
11	0.00	0.05	10.0	10.0
12	0.00	0.10	10.0	10.0

Table II shows the formulas evaluated as to stability of the LAA under ultraviolet radiation for 60 minutes. All the formulas contain propylene glycol, modified xanthane gum, Dequest 2010, PVA and water.

The purpose of the tests carried out with the compositions shown in Table II was to confirm that the stabilization of the LAA is successfully obtained with different reverting compounds.

Sodium dithionite was used in formulas 5, 8, 11 and 12, resulting in a percentage of remaining LAA of about 100% after 90 days, which means that LAA practically does not undergo any degradation during at least 90 days at room temperature, maintaining the initial concentrations of its molecular form.

The reverting compound employed in formulas 6, 7, 9 and 10 is Glutathion. From Figure 1, it can be noticed that the percentage of remaining LAA in formulas 6 and 7 remains around 100% even in the presence of another reverting compound,

Figure 2 shows the stability graph of compositions containing OPC, which is a grape seed oligomer, through which it is possible to measure the stability of said OPC.

- 5 It can be noticed that the OPC's stability under the sun light is of at least 70% and around 80% in the dark, that latter being the normal condition for the final commercial product, thus demonstrating that the result is favorable for the invention.

Example 2

A water-in-oil emulsion was prepared which comprises in a first phase:

Ingredient	% Mass	Function
Water	About 70	vehicle
Butylene glycol	1 to 4	Oxygen-removing compound
Glutathion	0.1	Oxidation reverting compound
1-Hydroethylidene (1,1-diphosphonic) acid Dequest ®	0.15	Metallic ion sequestering agent
LAA	from 1 to 30	Antioxidant agent
Grape seed OPC	0.3	Antioxidant agent

and, in a second phase

Ingredient	% Mass	Function
Glycerin	7.0	Hydrating agent
Lamellar Ceramides	1.0	Hydrating agent
Cetyl dimethicone copolyol	2.0	Emulsifier
Triglycerol isostearate 4	2.0	Emulsifier
Vitamin E	2.0	Antioxidant
Sodium benzoate	0.3	Preservative
Colloidal silicon dioxide	0.3	Thickening agent
Magnesium sulphate	0.7	Thickening agent
Cyclomethicone D5/d6	13.5	Emollient
Isohexadecane	5.0	Solvent

A panel was composed in a blind study, with 80 female volunteers with ages ranging between 25 and 65 years, evaluated at two different times: after the fifteenth day of use (T15) and at the 30th day of use (T30). The product was supplied at ratios of about 16:9 of the first phase to the second phase and according to the composition described in the example above. The results of this evaluation are given in table III where the expressed percentages refer to the percentage of users that perceived the occurrence of the corresponding benefit.

Table III - Evaluation of the product performance by the physician

	T15	T30
Wrinkles	16.6%	31.2%
Flaccidity	8.7%	16.6%
Drying	11.2%	63.7%
Rings under the eyes	17.5%	27.5%
Edema	12.5%	22.5%

Amongst the product beneficial effects, including those evaluated the test, the following should be stressed out:

- it alleviated the skin aging marks around the eyes, such as wrinkles and flaccidity;
- it reduced the dark rings and pockets under the eyes;
- it improved the stiffness of the skin;

CLAIMS

1. A process for stabilizing antioxidant compounds characterized by comprising the step of contacting said compound, in an aqueous medium, with an oxygen-removing compound, a metallic ion sequestering compound and an oxidation reaction reverting
5 compound.

2. A process in accordance with claim 1, characterized in that the antioxidant compound is selected from group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's)

3. A process in accordance with any one of claims 1 and 2, characterized
10 in that the antioxidant is LAA.

4. A process in accordance with claims 1 the 3, characterized in that the antioxidant comprises a further proantocianidine (OPC)

5. A process in accordance with any one of the previous claims characterized in that the oxygen-removing compound is a glycol.

15 6. A process in accordance with claim 5, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and mixtures thereof, more preferably propylene glycol.

7. A process in accordance with any one of the previous claims, characterized in that the metallic ion sequestering agent is selected from the group
20 consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates that include di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

8. A process in accordance with claim 7, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt
25 of 1-hydroxy ethylidene (1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra (methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta (methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate) acid and the mixtures thereof.

30 9. A process in accordance with claim 8, characterized in that the metallic ion sequestering agent is 1-hydroxy ethylidene (1,1-diphosphate) acid.

10. A process in accordance with any one of the previous claims characterized in that the oxidation reaction reverting compound is selected from the group consisting of sodium dithionite, sodium bisulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as the mixtures thereof.

5 11. A process in accordance with claim 10, characterized in that the oxidation reaction reverting compound is Glutathion or sodium dithionite.

12. A process in accordance with any one of the previous claims, characterized by comprising a first step of preparing an aqueous solution containing the oxygen-removing compound, the metallic ion sequestering agent and the
10 oxidation reaction reverting compound, and a second stage of adding the antioxidant to the thus prepared composition, in a aqueous medium.

13. A process in accordance with claim 12, characterized in fact of the composition formed in the first step comprises the oxygen-removing compound in a range from about 10% to about 25%, the metallic ion sequestering agent in a range
15 from about 0.01% to about 0.20%, the oxidation reaction reverting compound at a concentration of about 0.01% to about 0.5%, the content of the antioxidant being from about 0.01% to about 30%, all the percentages being by weight based on the total weight of the composition.

14. A process in accordance with claim 13, characterized in fact of the
20 composition formed in the first step comprises the oxygen-removing compound in a range from about 16% to about 19%, the metallic ion sequestering agent in a range from about 0.10% to about 0.20% and the oxidation reaction reverting compound at a concentration from about 0.05% to about 0.2%, the content of the antioxidant being from about 0.5% to about 20% by weight.

25 15. A process in accordance with claim 12, characterized in that the antioxidant is an OPC, and wherein said first composition also comprises LAA.

16. An aqueous composition comprising at least one antioxidant, characterized by further comprising an oxygen-removing compound, a metallic ion sequestering agent and an oxidation reaction reverting compound.

30 17. An aqueous composition in accordance with claim 16, characterized in that the antioxidant is selected from the group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's)

of an oxygen-removing compound, from about 0.01% to about 0.20% of a metallic ion sequestering agent, and from about 0.01% to about 0.5% of an oxidation reaction reverting compound.

28. A two-phase aqueous cosmetic composition, characterized by comprising, in a first phase, at least one antioxidant, an oxygen-removing compound, a metallic ion sequestering agent and an oxidation reaction reverting compound and, in a second phase, at least one hydrating compound.

29. A two-phase composition in accordance with claim 28, characterized in that the weight ratio between the first and second phases is from about 12:8 to 20:11.

30. A two-phase composition in accordance with claim 28 or 29, characterized in that said at least one antioxidant is selected from the group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's).

31. A two-phase composition in accordance with any one of claims 28 to 30 characterized in that the oxygen-removing compound is a glycol.

32. A two-phase composition in accordance with claim 31, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and the mixtures thereof, more preferably propylene glycol.

33. A two-phase composition in accordance with any one of claims 28 to 32, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates that include di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

34. A two-phase composition in accordance with claim 33, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxy ethylidene (1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra(methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta (methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate) acid and mixtures thereof.

35. A two-phase composition in accordance with claim 34, characterized in that the metallic ion sequestering agent is 1-hydroxy ethylidene (1,1-diphosphate)

18. An aqueous composition in accordance with any one of claims 16 and 17, characterized in that the antioxidant is LAA.

19. An aqueous composition in accordance with claims 16 the 17, characterized in that the antioxidant comprises proantocianidines (OPC's)

5 20. An aqueous composition in accordance with any one of the previous claims characterized in that the oxygen-removing compound is a glycol.

21. An aqueous composition in accordance with claim 20, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and mixtures thereof, more preferably propylene glycol.

10 22. An aqueous composition in accordance with any one of the previous claims, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates including di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

15 23. An aqueous composition in accordance with claim 22, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxy ethylidene (1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra (methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt
20 of diethylene diamine penta (methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate) acid and mixtures thereof.

24. An aqueous composition in accordance with claim 23, characterized in that the metallic ion sequestering agent is 1-hydroxy ethylidene (1,1-diphosphate) acid.

25 25. An aqueous composition in accordance with any one of the previous claims characterized in that the oxidation reaction reverting compound is selected from the group comprising sodium dithionite, sodium bissulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as mixtures thereof.

30 26. An aqueous composition in accordance with claim 25, characterized in that the oxidation reaction reverting compound is Glutathion or sodium dithionite.

27. An aqueous composition in accordance with claim 18, characterized by comprising from about 0.01% to about 30% of LAA, from about 10% to about 25%

acid.

36. A two-phase composition in accordance with any one of claims 28 to 35 characterized in that the oxidation reaction reverting compound is selected from the group comprising sodium dithionite, sodium bissulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as mixtures thereof.

37. An aqueous two-phase composition in accordance with claim 36, characterized in that the oxidation reaction reverting compound is Glutathion or sodium dithionite.

38. A two-phase composition in accordance with any one of claims 28 to 37, characterized in that the hydrating compound is glycerin.

39. A two-phase composition in accordance with any one of claims 28 to 37, characterized in that the second phase comprises ceramides in a liquid crystal emulsion form.

40. A two-phase composition in accordance with claim 39, characterized by comprising, in the first phase, an aqueous composition comprising an amount of 0.2 to 10% of ascorbic acid and about 0.001 to 2,2% of OPC's and, in the second phase, glycerin in a range from 1.0 to 10%, and 0.5 to 3,0% of ceramides contained in a liquid crystal emulsion, all percentages being based on the total weight of the composition.

41. A two-phase composition in accordance with any one of claims 28 to 40, characterized by further comprising, in its second phase, about 13 to 25% of emollients, about 1 to 4% of an anti-radical agent, about 0.001 to 0,3% of a preservative, and about 0.05 to 0,6% of a thickening agent.

42. A composition in accordance with any one of claims 28 to 41, characterized by being in the form of an homogeneous emulsion containing an emulsifying system comprising a first emulsifier selected from the group consisting of organosilicones and a second emulsifier having a molecular structure similar to that of skin lipids.

43. A composition in accordance with claim 42, characterized in that said organosilicone is cetyl dimethicone copolyol and the second emulsifier is polyglycerol-4-isostearate.

44. A composition in accordance with claim 42 or 43, characterized by

being in the form of micro-particles smaller than 3 μm .

45. A composition in accordance with claim 44, characterized in that the micro-particles have a size smaller than 1 μm .

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/BR 00/00078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 C09K15/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C09K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, FSTA, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 846 996 A (FALLICK HARRY) 8 December 1998 (1998-12-08)	1-3,5, 10,11, 16-18, 20,25,26 28
A	column 3, line 4 -column 4, line 10 ---	
X	US 5 023 235 A (N GUYEN QUANG L ET AL) 11 June 1991 (1991-06-11)	1-3,10, 11, 16-18, 25,26 28
A	column 1, line 60 -column 2, line 35 --- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/BR 00/00078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WINKLER, BARRY S.: "Unequivocal evidence in support of the nonenzymic redox coupling between glutathione/glutathione disulfide and ascorbic acid/dehydroascorbic acid" BIOCHIM. BIOPHYS. ACTA (1992), 1117(3), 287-90 , XP002152766 cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 288, column 1 -column 2 ---	28
Y	WO 99 07362 A (COSMETICOS NATURAL IND COM) 18 February 1999 (1999-02-18) cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
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A	US 5 140 043 A (PINNELL SHELDON R ET AL) 18 August 1992 (1992-08-18) column 3, line 18 -column 4, line 6 ---	1,16,28
A	WO 96 07396 A (JOHNSON & JOHNSON CONSUMER ;JOHNSON & JOHNSON MEDICAL K K (JP); LI) 14 March 1996 (1996-03-14) examples 1,12 ---	1,16,28
A	DATABASE WPI Section Ch, Week 199525 Derwent Publications Ltd., London, GB; Class B05, AN 1995-190139 XP002152767 & JP 07 107938 A (SANEIGEN FFI KK), 25 April 1995 (1995-04-25) abstract -----	28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Title: "A PROCESS FOR STABILIZING ANTIOXIDANT COMPOUNDS, AND
AQUEOUS COMPOSITIONS"

Field of the Invention

5 The present invention relates to an improved process for stabilizing antioxidant compounds useful in cosmetic and pharmaceutical compositions.

Background of the Invention

10 An antioxidant compound is any compound or mixture of compounds that, when in contact with the skin, is capable of protect the skin against the action of free radicals.

15 Antioxidant compounds such as levogyrous ascorbic acid (LAA), popularly known as "Vitamin C", and proantocianidines (OPC) are widely used in the pharmaceutical and cosmetic industry since, among other characteristics, they act against the free radicals that speed up the aging process and degeneration of the cells.

20 One of the greatest technical difficulties for the use of the above antioxidant compounds is their instability. The LAA, for example, can easily be oxidized in the presence of atmospheric air, metallic ions or water, thus being transformed into dehydroascorbic acid, in addition to other by-products resulting from the oxidation. Such transformation diminishes its physiological properties, mainly under use conditions where the compound is exposed to the atmospheric air, metallic ions and water such as, for example, when incorporated into a topic solution.

25 In a simplified way, the instability of an antioxidant is expressed as a decrease of its reducing ability before it is contacted with the skin. In the case of the LAA, its instability is expressed as a compound degradation reaction.

 In the case of the OPC's the instability occurs through an oligomerization reaction, followed by polymerization.

30 The LAA is often used in the form of its salts or esters due to this instability. The compositions prepared in this way attain stability for long periods of time.



Many studies have been carried out in order to obtain an aqueous composition containing stable antioxidant compounds. Some alternatives to stabilize LAA are described in Brazilian Patent Applications PI 9704418-0 and PI 9704728-7, filed by the same applicant of the present application. In said patent applications, processes for stabilizing levogyrous ascorbic acid (LAA) in a water-containing mean are disclosed comprising the step of contacting the LAA with at least one compound capable of forming hydrogen bridges with the LAA.

Another procedure known from the art for stabilizing antioxidants involves the association thereof with the compounds capable of reverting the decomposition reaction, the so-called "reverting compounds". Once again, considering the LAA, for example, said compounds revert the dehydroascorbic acid formation reaction. However, the stabilization through this process results in compositions unacceptable for cosmetic use and many times unsuitable for medicinal use, since the required stoichiometric amount of reverting compounds within the stoichiometry limits of the reaction must be too high so that the desired results could be attained. Since the reverting compounds usually are selected from sulfur-containing compounds, the high content thereof in the resultant compositions bring about an unpleasant odor and sometimes their use are even legally forbidden. For example, in a solution containing a concentration of 5% by weight of LAA, which is a concentration range generally used in cosmetic-pharmaceutical products, contents of approximately 20% by weight of reverting compound should be required to ensure the LAA stability.

Another prior art reference that can be cited and that teaches the use of reverting compounds, is a work published by Wrinkler, B.S. (Biochim, Biophy, Acta, 1117, 1992, pages 287 through 290), in which a compound is described (Glutathion) that can act as a reducer or reverting compound of dehydroascorbic acid by transforming same into ascorbic acid in the stoichiometric form. Through this work it was discovered that it was impossible to keep stoichiometric amounts of the components to produce a cosmetic composition since the Glutathion has an unpleasant odor which is a characteristic of sulphidric compounds.

Therefore, it is an object of the present invention to provide a process for stabilizing antioxidant compounds, that is, anti-free radicals or "anti-radicals", that



makes it possible to overcome the drawbacks common to the known processes, among which the ones that use the so-called reverting compounds and, in a special way, that can result in stable, cosmetically more pleasant and more efficient compositions, also suitable for pharmaceutical use.

5 **Summary of the Invention**

The present invention is directed to a process for stabilizing antioxidant compounds comprising the step of adding to said compound, in an aqueous medium, at least one oxygen-removing compound, at least one metallic ion sequestering compound and at least one oxidation reaction reverting compound.

10 The invention is also directed to compositions containing antioxidant compounds stabilized according to the above process.

Brief Description of the Drawings

Figure 1 shows a stability graph of compositions containing LAA according to formulas prepared in accordance with the invention during at least 90
15 days at room temperature.

Figure 2 shows the stability graph of compositions containing OPC that is an oligomer of grape seed, with which it is possible to measure the stability of said OPC.

Detailed Description of the Invention

20 The present inventors have now found out that the association of at least one antioxidant compound with an oxidation reaction reverting compound, in an aqueous medium, even without fulfilling the stoichiometry limits of the oxidation reaction, together with an oxygen-removing compound and a metallic ion sequestering agent, makes it possible to stabilize said antioxidant compound.

25 For the purposes of the present invention, some definitions of the terms used herein are given below.

An oxidation reaction reverting compound, or simply reverting compound, is to be understood as any compound or mixture of compounds having a higher oxidation potential than the oxidation potential of the oxidant to be stabilized
30 so that the concentration of antioxidant sub-compounds to be generated turns back to the original antioxidant in its molecular form.

As to the oxygen-removing compound, or simply oxygen remover, is any



compound or mixture of compounds capable of decreasing the oxygen solubility in a medium containing water and the antioxidant to be stabilized.

The metallic ion sequestering, or simply sequestering agent, is any compound or mixture of compounds having a high complexing constant and being effective for capturing and retaining such ions at pH values lower than 5.0. The effectiveness of the sequestering agent is defined by its ability to complexing the metallic ions present in a medium containing water and the antioxidant to be stabilized, so that it can minimize and preferably prevents the decomposition catalysis of any antioxidant present in said medium.

The invention is particularly suitable for providing the stabilization of compositions containing antioxidant compounds such as levogyrous ascorbic acid (LAA), or proantocianidines (OPC), or both, the resultant stability being effective for long periods of time.

In a first embodiment of the invention which is related to the stabilization of LAA in a aqueous medium, the oxygen-removing compound is selected from the group consisting of glycols, more preferably among propylene glycol and butylene glycol as well as mixtures thereof, even more preferably the propylene glycol.

The metallic ion sequestering compound, on its turn, is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates including di-, tri-, tetra- and pentavalent acids, the salts and mixtures thereof. More specifically the compound capable of sequestering metallic ions can be selected from the group consisting of sodium salt of 1-hydroxy ethylidene(1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra(methylenephosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta(methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate)acid, and mixtures thereof. Preferably, 1-hydroxy ethylidene(1,1-diphosphate) acid is used as the metallic ion sequestering agent, which is commercialized under the name Dequest 2010 supplied by MONSANTO.

In accordance with a preferred embodiment of the invention, the process for stabilizing antioxidant compounds comprises a first step wherein an aqueous solution containing the oxygen-removing compound and the metallic ion



sequestering agent at a ratio ranging from 2500:1 to 50:1 is prepared. In a second step, the antioxidant compound is then added to the resultant solution in a aqueous medium.

In a third step, a LAA oxidation reaction reverting compound is incorporated in the solution prepared in the first step described above, at a ratio ranging from 2520:1 to 20:1 related to the total mass of the oxygen-removing compound plus the sequestering agent mass, and at a ratio ranging from 1:0,02 to 3000:1, relating to the mass of the oxidizing compound. The great advantage achieved by the present invention is the notable stability of the LAA as time goes by. Compared to the compositions already known of the prior art containing this type of reverting compound, the invention allows the use of reverting compounds in significantly low amounts, thus making it possible to use same for cosmetic and/or pharmaceutical compositions, thus advantageously overcoming the aspect of unpleasant odor and the legal limitations concerning the concentration of reverting compounds.

Suitable oxidation reaction reverting compounds are those conventionally known for that purpose and include sulfur-containing compounds, preferably those selected from the group consisting of sodium dithionite, bisodium disulfites, calcium disulfites, potassium bisulfites and still more preferably Glutathion, as well as mixtures thereof.

Usually, for obtaining a commercially suitable cosmetic composition containing, for example, LAA as the antioxidant agent, the latter is used in a range from about 0.01% to about 30% and preferably from about 0.5% to about 20%, by weight, while the oxygen-removing compound is used in a range from about 10% to about 25%, preferably from about 16% to about 19%, and the sequestering agent is used in a range from about 0.01% to about 0.20%, preferably from about 0.10% to about 0.20%, all the percentages being by weight, based on the total weight of the composition. The oxidation reverting compound is present at a concentration from about 0.01% to about 0.5%, preferably from about 0.05% to about 0.2%. However, the amounts of these components will depend on the end uses for the resultant composition and should not limit the scope of the invention.

Among the antioxidant compounds of high importance in the cosmetic



and pharmaceutical industry, the OPC's can also be cited, and they are advantageously stabilized by the process of the present invention. Regarding those OPC's that can be stabilized by the process of the invention, a more preferred embodiment of the process comprises a first step of preparing a first composition
5 comprising the oxygen-removing compound, the sequestering agent and the oxidation reverting compound, which is then added to the OPC contained in an aqueous medium. In this preferred embodiment, the first composition contains other antioxidant, preferably the LAA.

Although the reasons are not yet fully defined, it was noticed that the
10 presence of another antioxidant having characteristics similar to LAA in the first composition favors the stabilization of the OPC's. Without being too theoretical, it is believed that there is a synergy between the LAA present and the OPC's, resulting in an advantageously stable composition.

In a particularly advantageous way, an aqueous composition containing
15 the stabilized antioxidant in accordance with the present invention is used in a two-phase cosmetic composition. This kind of composition comprises, in a first phase, at least one antioxidant compound, an oxygen-removing compound, a metallic ion sequestering compound and an oxidation reaction reverting compound and, in a second phase, at least one hydrating compound. Preferably, the first and second
20 phases are used at a weight ratio between them from 12:8 to 20:11, preferably of 16:9.

The two-phase composition described above has proved to be particularly suitable for regions where the skin is more delicate and, consequently, where it requires special care. "More delicate skin" must be understood as the one
25 more sensitive to the use of formulations that contain antioxidant compounds, emulsifying systems, fragrances, preservatives, cosmetic agents, among others. In the case of some antioxidant compounds, the use of high concentrations and the nature of these compounds can cause a higher exfoliation and irritation to the user skin and a discomfort sensation.

30 For example, the delicate region around the eyes as well as other areas of the body require special care since the skin is thinner and fragile. The skin structure in this region is different: the epidermis and dermis are thinner, thus being



more susceptible to the external aggressions and facilitating to the appearance of wrinkles and expression marks. Collagen and elastin, that contribute to a higher skin stiffness and elasticity are also present in a lower amounts that helps to characterize the delicacy of the region.

5 Hydrating agents as herein defined and useful for the present invention are those compounds or mixtures of compounds capable of increasing the water retention and restructuring the skin barrier for preventing the loss of water.

10 In a preferred way to formulate said two-phase composition, its first phase comprises an aqueous composition comprising an amount of 0.2 10%, preferably from 0.5 and 2%, of acid ascorbic and about 0.001 to 2.2%, preferably from 0.01 to 1.0%, of OPC's, particularly OPC from grape seed, and in its second phase a mixture of hydrating agents such as glycerin present at a cocentration of 1.0 to 10% and 0.5 to 3.0% of ceramides contained in a liquid crystal emulsion, also called lamellar ceramide.

15 The lamellar ceramides help to restore the skin protection barrier, thus reinforcing the skin structure and consequently preventing the excessive loss of water. Together with glycerin, which is a soft hydrating agent and that increases the retention of water by the skin, it improves the hydration and softness thereof. The high glycerin concentration also provides a high hydration potential.

20 In as still more preferred way, the two-phase composition containing antioxidants stabilized in accordance with the invention is in the form of a homogeneous emulsion comprising an emulsifying system including at least two emulsifiers, one of which is selected from the group consisting of organosilicones of the copolyol family, preferably cetyl dimethicone copolyol, and a second one the
25 molecular structure of which is similar to the natural skin lipids, preferably selected from a lipophylic stearic acid derived from a polyglycerol, more preferably polyglycerol-4-isostearate. The emulsifying system is advantageously added at a concentration of 0.5 to 8% by weight, based on the total weight of the composition.

30 In this emulsion form, the antioxidants together with the emulsifying system form micro-particles the size of which provides the emulsion with a better effectiveness and homogeneity. Since they are protected in micro-particles, the antioxidants, especially when it is OPC of grape seed, act on the walls of the blood



vessels reinforcing same, what contributes to reduce the appearance of dark rings under the eyes and avoid the formation of such dark rings. Preferably, the emulsion particles are smaller than 3 μm , more preferably smaller than 2 μm , and still more preferably smaller than 1 μm .

5 The cosmetic composition as herein described may also comprise in its second phase from 13 to 25%, preferably from about 16 to 22% of emollients, from about 1 to 4% of an anti-radical agent, more preferably from 1.5 to 3,5% of Vitamin E, from about 0.001 to 0,3% of a preservative, more preferably 0.01 to 0,3% of sodium benzoate, and from about 0.05 to 0,6% of a thickening agent, more
10 preferably from about 0.15 to 0,4% of colloidal silicon dioxide.

 It was observed that the selection of the preservative agent is an important factor for the stabilization of the emulsion micro-particles due to its stripping ratio between the water and oil phases.

 The illustrative examples and tests given below will better describe the
15 present invention. However, the illustrated data and procedures merely refer to some embodiments of the present invention and should not be understood as limiting the scope of the invention.

Example 1

 Comparative tests carried out by the inventors confirm the important
20 paper of the reverting compound in the stabilization of antioxidants as per information obtained by Wrinkler B. S. in his work cited herein. A first test was carried out in order to determine the degradation kinetics of a 10% LAA solution in water-containing medium (m/v) under ultraviolet radiation, using a ultraviolet spectrophotometer, for 60 minutes. An immediate degradation of the LAA was
25 observed, wherein a concentration of molecular LAA of about 9,58% (m/v) remained.

 A stoichiometric amount of the reverting compound of the oxidation reaction, that is, Glutathion, was added to the previous post-irradiated solution. The resultant solution was irradiated with ultraviolet radiation for further 60 minutes. By analyzing the remaining LAA, it could be noticed that 9,50% (m/v) thereof was still
30 present. Therefore, the degradation of the LAA is dramatically minimized after the reverting compound is added.

 In a third test, a 10% LAA solution was prepared in a water-containing



medium (m/v) with a stoichiometric amount of the oxidation reaction reverting compound Glutathion. The solution was irradiated with ultraviolet radiation for 60 minutes. By analyzing the remaining LAA, a high content of 9.98% (m/v) was attained, thus confirming that the reverting compound inhibits the degradation of LAA. However, the use of said compound in stoichiometric amounts still presents the already mentioned disadvantages.

For the purpose of evaluating the invention, stability tests of the antioxidants LAA and LAA associated with OPC's in a water-containing medium have been carried out. Twelve different formulas were prepared in accordance with the invention, the chemical compositions of which as well as the obtained results are discussed in the following Tables I and II.

Table I

Formula	Glutathion (%) m/v) Reverting compound	OPC (%) m/v) Antioxidant	LAA (%) m/v) Antioxidant	Remaining LAA (%) m/v)
1	0.05	0	10	9.82
2	0.10	0	10	9.92
3	0.05	2	10	9.82
4	0.10	2	10	10.00

Table I shows the stability results of the LAA and OPC's measured by the respective remaining percentages, wherein formulas 1 through 4 have been prepared in accordance with the invention: formulas 1 and 2 including only LAA and formulas 3 and 4 comprising LAA associated with OPC's.

In the above tests, formulas 1 through 4 also comprise propylene glycol as an oxygen-removing compound, 2010 Dequest as the metallic ion sequestering agent and water.

It can be noticed from Table I that formulas 1 through 4 prepared in accordance with the invention show a LAA stability very close to 100% compared with the initial concentration.

Next, tests with further eight formulas have been carried out to evaluate



the stability of LAA plus a gelling agent (Modified Xanthane Gum). Formulas 5, 8, 11 and 12 include sodium dithionite as an oxidation reaction reverting compound, and formulas 6, 7, 9 and 10 use, again, Glutathion as the reverting compound, as shown in Table II

5

Table II

Formulas	Glutathion (% m/v) Reverting compound	Sodium dithionite (% m/v) Reverting compound	LAA (% m/v) Antioxidant	Remaining LAA (% m/v)
5	0.00	0.05	5.0	5.0
6	0.10	0.00	5.0	5.0
7	0.05	0.00	5.0	5.0
8	0.00	0.10	5.0	5.0
9	0.05	0.00	10.0	10.0
10	0.10	0.00	10.0	10.0
11	0.00	0.05	10.0	10.0
12	0.00	0.10	10.0	10.0

Table II shows the formulas evaluated as to stability of the LAA under ultraviolet radiation for 60 minutes. All the formulas contain propylene glycol, modified xanthane gum, Dequest 2010, PVA and water.

10 The purpose of the tests carried out with the compositions shown in Table II was to confirm that the stabilization of the LAA is successfully obtained with different reverting compounds.

15 Sodium dithionite was used in formulas 5, 8, 11 and 12, resulting in a percentage of remaining LAA of about 100% after 90 days, which means that LAA practically does not undergo any degradation during at least 90 days at room temperature, maintaining the initial concentrations of its molecular form.

The reverting compound employed in formulas 6, 7, 9 and 10 is Glutathion. From Figure 1, it can be noticed that the percentage of remaining LAA in formulas 6 and 7 remains around 100% even in the presence of another reverting compound,



Figure 2 shows the stability graph of compositions containing OPC, which is a grape seed oligomer, through which it is possible to measure the stability of said OPC.

- 5 It can be noticed that the OPC's stability under the sun light is of at least 70% and around 80% in the dark, that latter being the normal condition for the final commercial product, thus demonstrating that the result is favorable for the invention.

Example 2

A water-in-oil emulsion was prepared which comprises in a first phase:

Ingredient	% Mass	Function
Water	About 70	vehicle
Butylene glycol	1 to 4	Oxygen-removing compound
Glutathion	0.1	Oxidation reverting compound
1-Hydroethylidene (1,1-diphosphonic) acid Dequest ®	0.15	Metallic ion sequestering agent
LAA	from 1 to 30	Antioxidant agent
Grape seed OPC	0.3	Antioxidant agent

and, in a second phase

Ingredient	% Mass	Function
Glycerin	7.0	Hydrating agent
Lamellar Ceramides	1.0	Hydrating agent
Cetyl dimethicone copolyol	2.0	Emulsifier
Triglycerol isostearate 4	2.0	Emulsifier
Vitamin E	2.0	Antioxidant
Sodium benzoate	0.3	Preservative
Colloidal silicon dioxide	0.3	Thickening agent
Magnesium sulphate	0.7	Thickening agent
Cyclomethicone D5/d6	13.5	Emollient
Isohexadecane	5.0	Solvent



A panel was composed in a blind study, with 80 female volunteers with ages ranging between 25 and 65 years, evaluated at two different times: after the fifteenth day of use (T15) and at the 30th day of use (T30). The product was supplied at ratios of about 16:9 of the first phase to the second phase and according to the composition described in the example above. The results of this evaluation are given in table III where the expressed percentages refer to the percentage of users that perceived the occurrence of the corresponding benefit.

Table III - Evaluation of the product performance by the physician

	T15	T30
Wrinkles	16.6%	31.2%
Flaccidity	8.7%	16.6%
Drying	11.2%	63.7%
Rings under the eyes	17.5%	27.5%
Edema	12.5%	22.5%

Amongst the product beneficial effects, including those evaluated the test, the following should be stressed out:

- it alleviated the skin aging marks around the eyes, such as wrinkles and flaccidity;
- it reduced the dark rings and pockets under the eyes;
- it improved the stiffness of the skin;



CLAIMS

1. A process for stabilizing antioxidant compounds characterized by comprising the step of contacting said compound, in an aqueous medium, with an oxygen-removing compound, a metallic ion sequestering compound and an oxidation reaction reverting
5 compound.

2. A process in accordance with claim 1, characterized in that the antioxidant compound is selected from group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's)

3. A process in accordance with any one of claims 1 and 2, characterized
10 in that the antioxidant is LAA.

4. A process in accordance with claims 1 the 3, characterized in that the antioxidant comprises a further proantocianidine (OPC)

5. A process in accordance with any one of the previous claims characterized in that the oxygen-removing compound is a glycol.

15 6. A process in accordance with claim 5, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and mixtures thereof, more preferably propylene glycol.

7. A process in accordance with any one of the previous claims, characterized in that the metallic ion sequestering agent is selected from the group
20 consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates that include di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

8. A process in accordance with claim 7, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt
25 of 1-hydroxy ethylidene (1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra (methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta (methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate) acid and the mixtures thereof.

30 9. A process in accordance with claim 8, characterized in that the metallic ion sequestering agent is 1-hydroxy ethylidene (1,1-diphosphate) acid.



10. A process in accordance with any one of the previous claims characterized in that the oxidation reaction reverting compound is selected from the group consisting of sodium dithionite, sodium bisulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as the mixtures thereof.

5 11. A process in accordance with claim 10, characterized in that the oxidation reaction reverting compound is Glutathion or sodium dithionite.

12. A process in accordance with any one of the previous claims, characterized by comprising a first step of preparing an aqueous solution containing the oxygen-removing compound, the metallic ion sequestering agent and the
10 oxidation reaction reverting compound, and a second stage of adding the antioxidant to the thus prepared composition, in a aqueous medium.

13. A process in accordance with claim 12, characterized in fact of the composition formed in the first step comprises the oxygen-removing compound in a range from about 10% to about 25%, the metallic ion sequestering agent in a range
15 from about 0.01% to about 0.20%, the oxidation reaction reverting compound at a concentration of about 0.01% to about 0.5%, the content of the antioxidant being from about 0.01% to about 30%, all the percentages being by weight based on the total weight of the composition.

14. A process in accordance with claim 13, characterized in fact of the
20 composition formed in the first step comprises the oxygen-removing compound in a range from about 16% to about 19%, the metallic ion sequestering agent in a range from about 0.10% to about 0.20% and the oxidation reaction reverting compound at a concentration from about 0.05% to about 0.2%, the content of the antioxidant being from about 0.5% to about 20% by weight.

25 15. A process in accordance with claim 12, characterized in that the antioxidant is an OPC, and wherein said first composition also comprises LAA.

16. An aqueous composition comprising at least one antioxidant, characterized by further comprising an oxygen-removing compound, a metallic ion sequestering agent and an oxidation reaction reverting compound.

30 17. An aqueous composition in accordance with claim 16, characterized in that the antioxidant is selected from the group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's)



18. An aqueous composition in accordance with any one of claims 16 and 17, characterized in that the antioxidant is LAA.

19. An aqueous composition in accordance with claims 16 the 17, characterized in that the antioxidant comprises proantocianidines (OPC's)

5 20. An aqueous composition in accordance with any one of the previous claims characterized in that the oxygen-removing compound is a glycol.

21. An aqueous composition in accordance with claim 20, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and mixtures thereof, more preferably propylene glycol.

10 22. An aqueous composition in accordance with any one of the previous claims, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates including di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

15 23. An aqueous composition in accordance with claim 22, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxy ethylidene (1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra (methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt
20 of diethylene diamine penta (methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate) acid and mixtures thereof.

24. An aqueous composition in accordance with claim 23, characterized in that the metallic ion sequestering agent is 1-hydroxy ethylidene (1,1-diphosphate) acid.

25 25. An aqueous composition in accordance with any one of the previous claims characterized in that the oxidation reaction reverting compound is selected from the group comprising sodium dithionite, sodium bissulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as mixtures thereof.

30 26. An aqueous composition in accordance with claim 25, characterized in that the oxidation reaction reverting compound is Glutathion or sodium dithionite.

27. An aqueous composition in accordance with claim 18, characterized by comprising from about 0.01% to about 30% of LAA, from about 10% to about 25%



of an oxygen-removing compound, from about 0.01% to about 0.20% of a metallic ion sequestering agent, and from about 0.01% to about 0.5% of an oxidation reaction reverting compound.

28. A two-phase aqueous cosmetic composition, characterized by comprising, in a first phase, at least one antioxidant, an oxygen-removing compound, a metallic ion sequestering agent and an oxidation reaction reverting compound and, in a second phase, at least one hydrating compound.

29. A two-phase composition in accordance with claim 28, characterized in that the weight ratio between the first and second phases is from about 12:8 to 20:11.

30. A two-phase composition in accordance with claim 28 or 29, characterized in that said at least one antioxidant is selected from the group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's).

31. A two-phase composition in accordance with any one of claims 28 to 30 characterized in that the oxygen-removing compound is a glycol.

32. A two-phase composition in accordance with claim 31, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and the mixtures thereof, more preferably propylene glycol.

33. A two-phase composition in accordance with any one of claims 28 to 32, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates that include di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

34. A two-phase composition in accordance with claim 33, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxy ethylidene (1,1-diphosphate) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra(methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta (methylene phosphonic) acid, hydroxy ethylidene(1,1-diphosphate) acid and mixtures thereof.

35. A two-phase composition in accordance with claim 34, characterized in that the metallic ion sequestering agent is 1-hydroxy ethylidene (1,1-diphosphate)



acid.

36. A two-phase composition in accordance with any one of claims 28 to 35 characterized in that the oxidation reaction reverting compound is selected from the group comprising sodium dithionite, sodium bissulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as mixtures thereof.

37. An aqueous two-phase composition in accordance with claim 36, characterized in that the oxidation reaction reverting compound is Glutathion or sodium dithionite.

38. A two-phase composition in accordance with any one of claims 28 to the 37, characterized in that the hydrating compound is glycerin.

39. A two-phase composition in accordance with any one of claims 28 to 37, characterized in that the second phase comprises ceramides in a liquid crystal emulsion form.

40. A two-phase composition in accordance with claim 39, characterized by comprising, in the first phase, an aqueous composition comprising an amount of 0.2 to 10% of ascorbic acid and about 0.001 to 2,2% of OPC's and, in the second phase, glycerin in a range from 1.0 to 10%, and 0.5 to 3,0% of ceramides contained in a liquid crystal emulsion, all percentages being based on the total weight of the composition.

41. A two-phase composition in accordance with any one of claims 28 to 40, characterized by further comprising, in its second phase, about 13 to 25% of emollients, about 1 to 4% of an anti-radical agent, about 0.001 to 0,3% of a preservative, and about 0.05 to 0,6% of a thickening agent.

42. A composition in accordance with any one of claims 28 to 41, characterized by being in the form of an homogeneous emulsion containing an emulsifying system comprising a first emulsifier selected from the group consisting of organosilicones and a second emulsifier having a molecular structure similar to that of skin lipids.

43. A composition in accordance with claim 42, characterized in that said organosilicone is cetyl dimethicone copolyol and the second emulsifier is polyglycerol-4-isostearate.

44. A composition in accordance with claim 42 or 43, characterized by



being in the form of micro-particles smaller than 3 μm .

45. A composition in accordance with claim 44, characterized in that the micro-particles have a size smaller than 1 μm .



INTERNATIONAL SEARCH REPORT

International Application No

PC 1/95/11750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 586 106 (JOHNSON & JOHNSON CONSUMER PRODUCTS) 9 March 1994 see page 4, line 50 - page 6, line 45; table 1 ---	1-41,56
X	EP,A,0 440 398 (JOHNSON & JOHNSON CONSUMER PRODUCTS) 7 August 1991 see example 2 ---	1-41,56
X	EP,A,0 343 444 (BAYER) 29 November 1989 see ---	1-41,56
X	EP,A,0 330 496 (BEECHAM GROUP) 30 August 1989 cited in the application see ---	1-41,56
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

15 February 1996

Date of mailing of the international search report

21.05.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

FISCHER, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/11750

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO,A,95 25507 (PIERRE FABRE DERMO-COSMETIQUE) 28 September 1995 see the whole document -----</p>	1-41

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 11750

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. CLAIMS 1-41 AND 56
2. CLAIMS 42-54
3. CLAIM 55

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-41 AND 56

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US95/ 11750

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

LACK OF UNITY OF INVENTION

No.	Searched	Subject
1	yes	Claims 1-41 and 56: A skin care composition
2	no	Claims 42-54: A two-compartment container
3	no	Claim 55: A method of storing a composition

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Rule 13.1 PCT deals with the requirement of unity of invention and states the principle that an international application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept. Rule 13.2 PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.

LACK OF UNITY OF INVENTION A PRIORI

The first problem underlying the present application consists of providing a skin care composition comprising certain specified retinoids stabilized against chemical (i.e. oxidative) degradation.

The proposed solution consists of incorporating those compounds into oil-in-water emulsions comprising a specific stabilizing system (claims 1-41 and 56). The special technical feature, defining the contribution which this invention, considered as a whole, makes over the prior art is to be seen in the specific stabilizing system.

The subject matter of claims 42-54 (a two-compartment container) may be used in relation to the skin care composition of claims 1-41 and 56.

This container, however is not effectively specifically designed for containing the skin care composition of claims 1-41 and 56. As a container it can be employed in a variety of uses, including pharmaceutical uses, and other uses which are not restricted to skin care compositions. Moreover, the components of the composition referred to in claims 42-52 and 54 are not restricted to the retinoids specified in claim 1, but may include any retinoid.

As such the subject matter of claims 42-54 lacks a common special technical feature with the subject matter of claims 1-41 and 56.

The second problem underlying the present application is to be seen in the provision of a two-compartment container in which its contents are out of contact with oxygen. The solution to this second problem is the provision of the container defined in claims 42-54. The special technical feature, defining the contribution which this invention, considered as a whole, makes over the prior art is to be seen in the particular features of the container. There is no technical relationship in the above sense with the first

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US95/11750

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

mentioned problem and its solution.

The subject matter of claim 55 (a method of storing a composition in a two-compartment container) may be used in relation to the skin care composition of claims 1-41 and 56, and in relation to the subject matter of claims 42-54.

This method, however is not effectively specifically designed for storing the skin-care composition defined in claims 1-41 and 56. As a method it can be employed for storing a variety of compositions (including pharmaceutical compositions) in a variety of two-compartment containers (regardless whether contact with oxygen is to be avoided or not). Moreover, the skin care composition referred to in claim 55 is not restricted to the skin care composition specified in claim 1, but may include any skin care composition.

As such the subject matter of claim 55 lacks a common special technical feature with the subject matter of claims 1-41 and 56, and 42-54, respectively.

There is no technical relationship in the above sense with the first and second mentioned problems and their solutions. The problem underlying the subject matter of claim 55 must be defined as to provide a method of storing a composition in a two-compartment container. The special technical feature, defining the contribution which this invention, considered as a whole, makes over the prior art is to be seen in the particular features of the method.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed in the communication pursuant to Article 17(3)(a) PCT. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Searching these different subjects would have caused major additional searching efforts.

Only the first subject was searched.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC 95/11750

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0586106	09-03-94	AU-B-	4444893	10-02-94
		BR-A-	9303269	08-03-94
		CA-A-	2101101	07-02-94
		GR-A-	93100292	29-04-94
		JP-A-	7291847	07-11-95

EP-A-0440398	07-08-91	AU-B-	639063	15-07-93
		AU-B-	6997291	01-08-91
		CA-A-	2035086	30-07-91
		DE-D-	69100848	10-02-94
		DE-T-	69100848	11-05-94
		ES-T-	2048557	16-03-94
		HK-A-	94994	16-09-94
		JP-A-	4210902	03-08-92
		SG-A-	77794	14-10-94

EP-A-0343444	29-11-89	DE-A-	3817623	30-11-89

EP-A-0330496	30-08-89	AU-B-	3072989	31-08-89
		DE-D-	68909970	25-11-93
		DE-T-	68909970	10-02-94
		ES-T-	2059721	16-11-94
		JP-A-	2059518	28-02-90

WO-A-9525507	28-09-95	FR-A-	2717686	29-09-95
		AU-B-	2140895	09-10-95

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DANNEMANN, SIEMSEN, BIGLER & IPANEM
A MOREIRA
Rua Marques de Olinda, 70
Caixa Postal 2142
CEP-22251-040 Rio de Janeiro, RJ
BRESIL

PCT

WRITTEN OPINION

(PCT Rule 66)

- 3 400 15 2 3 8 1
BIGLER & L. MOREIRA

Date of mailing (day/month/year)		31.07.2001
Applicant's or agent's file reference PE-3929		REPLY DUE within 1 month(s) and 15 days from the above date of mailing
International application No. PCT/BR00/00078	International filing date (day/month/year) 14/07/2000	Priority date (day/month/year) 16/07/1999
International Patent Classification (IPC) or both national classification and IPC A61K7/48		
Applicant INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.		


- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
 - ☒ Basis of the opinion
 - ☐ Priority
 - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain document cited
 - ☒ Certain defects in the international application
 - ☒ Certain observations on the international application
- The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 16/11/2001.

Name and mailing address of the international preliminary examining authority:	Authorized officer / Examiner
 European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Pregetter, M
	Formalities officer (incl. extension of time limits) Longo, E Telephone No. +49 89 2399 8141



Henrique

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets* which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

Description, pages:

1-12 as originally filed

Claims, No.:

1-45 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

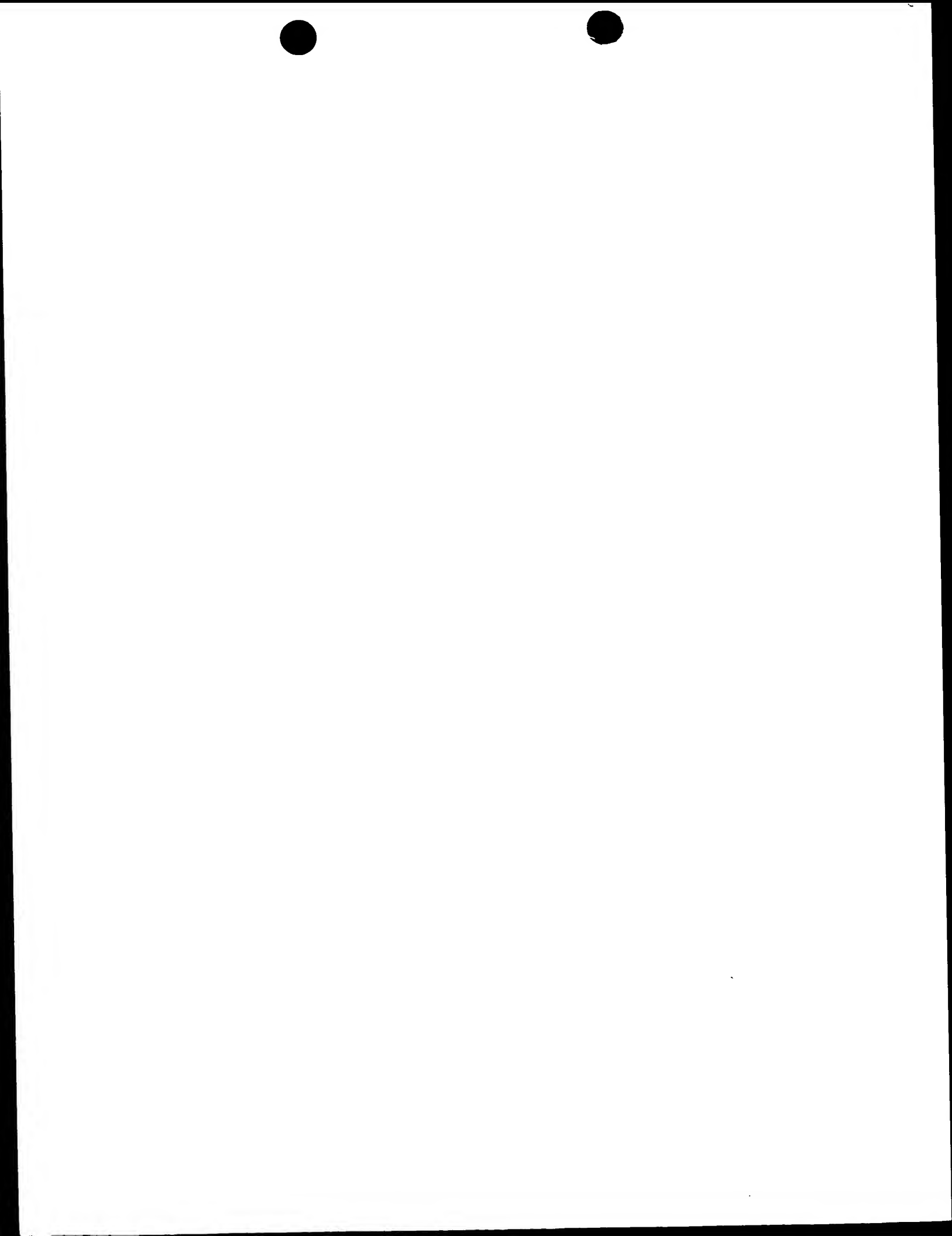
- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:



5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Claims 1-45

Inventive step (IS) Claims

Industrial applicability (IA) Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
 - ↘ D1: US-A-5 804 168 (MURAD HOWARD) 8 September 1998 (1998-09-08)
 - ↘ D2: WO 99 33439 A (ROBERTS RICHARD L ; GREENE JAMES A (US); SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08)
 - ↘ D3: US-A-5 902 591 (HERSTEIN MORRIS) 11 May 1999 (1999-05-11)
2. The subject-matter of present claim 1 is not novel according to Article 33(2) PCT. A process of contacting several compounds in aqueous medium necessarily takes place, when said compounds are all contained in the same aqueous solution/dispersion. Consequently, the same argumentation as given under point 3 applies.
3. The subject-matter of present claim 16 is not novel according to Article 33(2) PCT. D2 describes an oil-in-water formulation comprising an antioxidant compound in the aqueous phase (magnesium ascorbyl phosphate), a deoxygenating compound/oxygen removing compound (the most common humectants are glycols, which are given as examples of deoxygenating compounds), a metallic ions sequestering agent, a reducing agent (superoxide dismutase), and, in the dispersed phase, immunomodulator (beta glucan) and moisturizers/emollients (e.g. example 6). D3 discloses a mixture of 5% powdered ascorbic acid with 95% of an emulsion resulting in dissolving the ascorbic acid in the aqueous phase of said emulsion. The resulting aqueous phase comprises the ascorbic acid (antioxidant), a deoxygenating agent (butylene glycol), a metallic ions sequestering compound (EDTA) and a reducing agent (superoxide dismutase).
4. The subject-matter of present claim 28 is not novel according to Article 33(2) PCT. D2 describes an oil-in-water formulation comprising an antioxidant compound in the aqueous phase (magnesium ascorbyl phosphate), a deoxygenating compound (the most common humectants are glycols), a metallic ions

sequestering agent and a reducing agent (superoxide dismutase), and, in the dispersed phase moisturizers/emollients (hydrating comp.). Proanthocyanidins in the form of grape seed extract are also present (e.g. example 6).

5. With regard to the dependent claims, it is noted that a positive opinion can only be given, if dependent claims refer to independent claims that meet the requirements of the PCT.

Furthermore, the following has to be noted:

The use of a substance in certain percentages can only be considered to involve an inventive step, if it can be clearly shown that said percentages are unusual in the art and lead to a surprising effect.

The use of a specific immunomodulator, reducing agent, sequestering agent, ... can only be considered to involve an inventive step, if such a use is unusual in the art and leads to a surprising effect. However, the combination of specific compounds in specific percentages is very often not suggested by the prior art.

6. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

In case of non-compliance, said amendments cannot be taken into account when establishing the international preliminary examination report.

Re Item VII

Certain defects in the international application

1. According to Rule 10(f) PCT the beginning of a decimal fraction has to be marked by a period.
2. The description is not in conformity with claims 10-15, 25, 26, 36-39 as required by Rule 5.1(a)(iii) PCT.

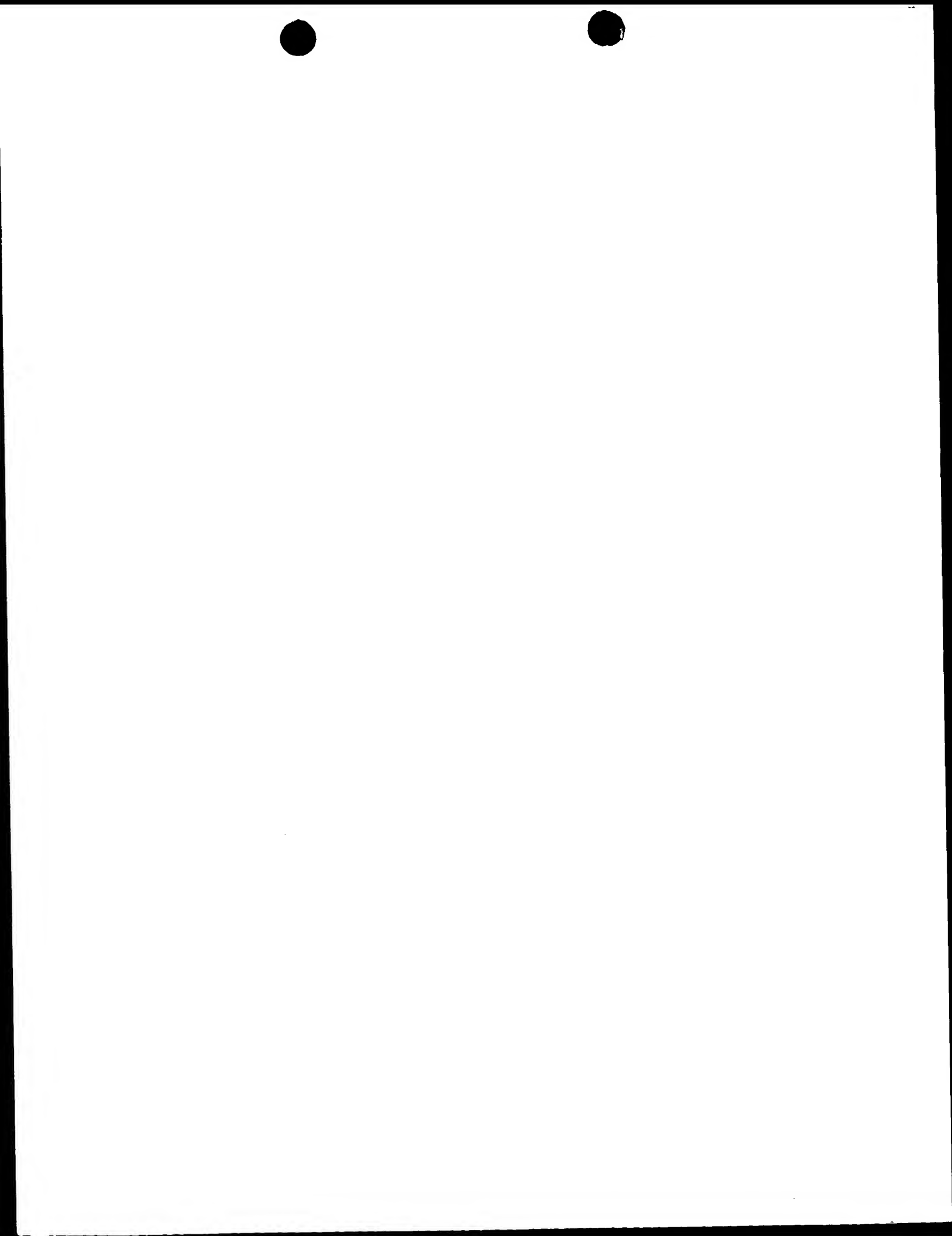
Re Item VIII



Certain observations on the international application

1. The term "preferably" does not limit the scope of a claim in any way.
However, excessive use of the term "preferably" can lead to a lack of clarity according to Article 6 PCT.
2. The use of parenthesis and abbreviations in claims leads to a lack of clarity (Article 6 PCT).
3. Present claim 8 cannot depend on claim 7, since claim 7 does not define the presence of a "phosphate". The same applies to claims 22 and 23 and 33/34
4. Claims 20,23 and 25 cannot be dependent on "any one of the previous claims", since claims 1-15 are process claims and a claim can only be dependent on a claim of the same category.
5. Claim 4 should probably read: "1 to 3" and "comprises further a proanthocyandine".
6. Claim 15, which is dependent on claim 12 refers to a "first composition". Claim 12 does not define a "first composition". Consequently, the subject-matter of claim 15 is not clear (Article 6 PCT).
7. Claim 38 defines glycerin as the hydration compound. The compound agent, according to claim 28 is in the "second phase". It is not clear, why glycerin should be present in the "second phase" and remain there, when chemically similar compounds, such as propylene glycol, are in the "first phase" (aqueous).
8. The terms "oxygen removing compound" and "oxidation reaction reverting compound" are unusual in the art.
The term "oxygen removing compound" has been understood to be a compound that diminishes the oxygen solubility in the medium.
The term "oxidation reaction reverting compound" has been understood to be a reducing agent.

9. The applicant is invited to clearly define what is meant by the term "two-phase" and to clearly point out which compounds are present in which phase.



INTERNATIONAL SEARCH REPORT

International Classification No

PCT/BR 00/00078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 C09K15/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C09K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, FSTA, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 846 996 A (FALLICK HARRY) 8 December 1998 (1998-12-08)	1-3,5, 10,11, 16-18, 20,25,26 28
A	column 3, line 4 -column 4, line 10 ---	
X	US 5 023 235 A (N GUYEN QUANG L ET AL) 11 June 1991 (1991-06-11)	1-3,10, 11, 16-18, 25,26 28
A	column 1, line 60 -column 2, line 35 --- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 November 2000

Date of mailing of the international search report

01/12/2000

Name and mailing address of the ISA

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Authorized officer

Shade, M



INTERNATIONAL SEARCH REPORT

International Application No

PCT/BR 00/00078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WINKLER, BARRY S.: "Unequivocal evidence in support of the nonenzymic redox coupling between glutathione/glutathione disulfide and ascorbic acid/dehydroascorbic acid" BIOCHIM. BIOPHYS. ACTA (1992), 1117(3), 287-90, XP002152766 cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 288, column 1 -column 2 ---	28
Y	WO 99 07362 A (COSMETICOS NATURAL IND COM) 18 February 1999 (1999-02-18) cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 11, line 5 -page 16, line 2 ---	28
A	US 5 140 043 A (PINNELL SHELDON R ET AL) 18 August 1992 (1992-08-18) column 3, line 18 -column 4, line 6 ---	1,16,28
A	WO 96 07396 A (JOHNSON & JOHNSON CONSUMER ;JOHNSON & JOHNSON MEDICAL K K (JP); LI) 14 March 1996 (1996-03-14) examples 1,12 ---	1,16,28
A	DATABASE WPI Section Ch, Week 199525 Derwent Publications Ltd., London, GB; Class B05, AN 1995-190139 XP002152767 & JP 07 107938 A (SANEIGEN FFI KK), 25 April 1995 (1995-04-25) abstract -----	28



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/BR 00/00078

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5846996	A	08-12-1998	US 5945447 A	31-08-1999
US 5023235	A	11-06-1991	FR 2610626 A	12-08-1988
			DE 3870001 A	21-05-1992
			DE 280606 T	11-05-1989
			EP 0280606 A	31-08-1988
			JP 63225689 A	20-09-1988
WO 9907362	A	18-02-1999	BR 9704418 A	30-03-1999
			BR 9704728 A	06-06-2000
			EP 0949919 A	20-10-1999
			US 6037481 A	14-03-2000
US 5140043	A	18-08-1992	AT 156355 T	15-08-1997
			AU 647699 B	24-03-1994
			AU 5523990 A	16-11-1990
			CA 2054189 A	18-10-1990
			DE 69031219 D	11-09-1997
			DE 69031219 T	22-01-1998
			DK 486499 T	16-03-1998
			EP 0486499 A	27-05-1992
			ES 2104605 T	16-10-1997
			HK 1001834 A	10-07-1998
			JP 4507089 T	10-12-1992
			WO 9012572 A	01-11-1990
WO 9607396	A	14-03-1996	AU 3633295 A	27-03-1996
			JP 8193019 A	30-07-1996
			US 6080393 A	27-06-2000
JP 7107938	A	25-04-1995	NONE	



11

11

11

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PE-3929	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/BR 00/ 00078	International filing date (day/month/year) 14/07/2000	(Earliest) Priority Date (day/month/year) 16/07/1999
Applicant IND*STRIA E COM RCIO DE COSM TICOS NATURA LTDA.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.



A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48 C09K15/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C09K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, FSTA, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 846 996 A (FALLICK HARRY) 8 December 1998 (1998-12-08)	1-3,5, 10,11, 16-18, 20,25,26 28
A	column 3, line 4 -column 4, line 10 ---	
X	US 5 023 235 A (N GUYEN QUANG L ET AL) 11 June 1991 (1991-06-11)	1-3,10, 11, 16-18, 25,26 28
A	column 1, line 60 -column 2, line 35 --- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

14 November 2000

Date of mailing of the international search report

01/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Shade, M



C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WINKLER, BARRY S.: "Unequivocal evidence in support of the nonenzymic redox coupling between glutathione/glutathione disulfide and ascorbic acid/dehydroascorbic acid" BIOCHIM. BIOPHYS. ACTA (1992), 1117(3), 287-90 , XP002152766 cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 288, column 1 -column 2 ---	28
Y	WO 99 07362 A (COSMETICOS NATURAL IND COM) 18 February 1999 (1999-02-18) cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 11, line 5 -page 16, line 2 ---	28
A	US 5 140 043 A (PINNELL SHELDON R ET AL) 18 August 1992 (1992-08-18) column 3, line 18 -column 4, line 6 ---	1,16,28
A	WO 96 07396 A (JOHNSON & JOHNSON CONSUMER ;JOHNSON & JOHNSON MEDICAL K K (JP); LI) 14 March 1996 (1996-03-14) examples 1,12 ---	1,16,28
A	DATABASE WPI Section Ch, Week 199525 Derwent Publications Ltd., London, GB; Class B05, AN 1995-190139 XP002152767 & JP 07 107938 A (SANEIGEN FFI KK), 25 April 1995 (1995-04-25) abstract -----	28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/ 00/00078

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5846996 A	08-12-1998	US 5945447 A	31-08-1999
US 5023235 A	11-06-1991	FR 2610626 A	12-08-1988
		DE 3870001 A	21-05-1992
		DE 280606 T	11-05-1989
		EP 0280606 A	31-08-1988
		JP 63225689 A	20-09-1988
WO 9907362 A	18-02-1999	BR 9704418 A	30-03-1999
		BR 9704728 A	06-06-2000
		EP 0949919 A	20-10-1999
		US 6037481 A	14-03-2000
US 5140043 A	18-08-1992	AT 156355 T	15-08-1997
		AU 647699 B	24-03-1994
		AU 5523990 A	16-11-1990
		CA 2054189 A	18-10-1990
		DE 69031219 D	11-09-1997
		DE 69031219 T	22-01-1998
		DK 486499 T	16-03-1998
		EP 0486499 A	27-05-1992
		ES 2104605 T	16-10-1997
		HK 1001834 A	10-07-1998
		JP 4507089 T	10-12-1992
		WO 9012572 A	01-11-1990
WO 9607396 A	14-03-1996	AU 3633295 A	27-03-1996
		JP 8193019 A	30-07-1996
		US 6080393 A	27-06-2000
JP 7107938 A	25-04-1995	NONE	



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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

DANNEMANN, SIEMSEN, BIGLER &
IPANEMA MOREIRA
Caixa Postal 2142
22251-040 - Rio de Janeiro - RJ
BRAZIL

Date of mailing
(day/month/year)

01/12/2000

Applicant's or agent's file reference

PE-3929

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/BR 00/00078

International filing date
(day/month/year)

14/07/2000

Applicant

INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Alex Schmidt

Gustavo



These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.



The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

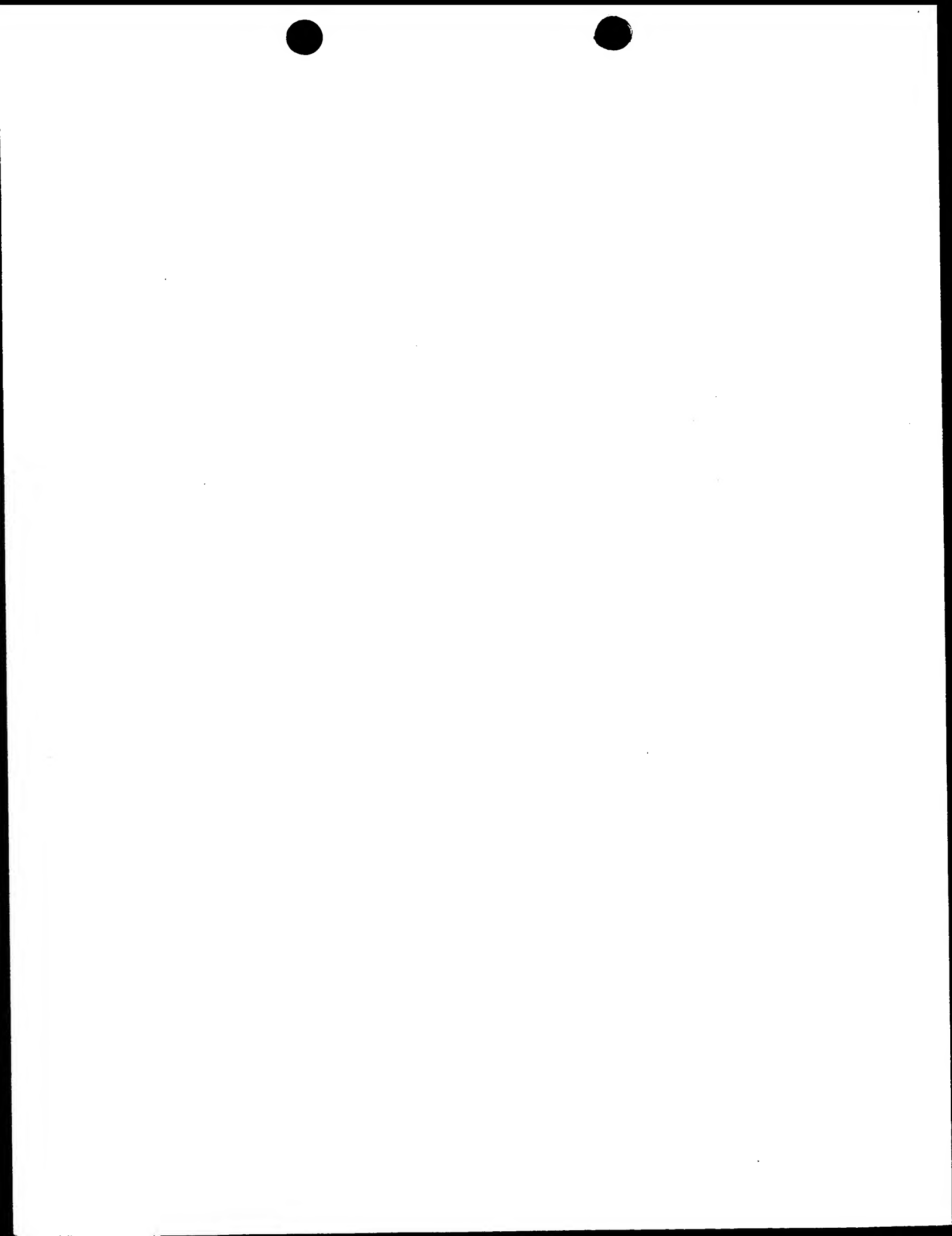
Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.



PATENT COOPERATION TREATY
PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PE-3929	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/BR 00/ 00078	International filing date (day/month/year) 14/07/2000	(Earliest) Priority Date (day/month/year) 16/07/1999
Applicant INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 C09K15/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C09K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, FSTA, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 846 996 A (FALLICK HARRY) 8 December 1998 (1998-12-08)	1-3,5, 10,11, 16-18, 20,25,26 28
A	column 3, line 4 -column 4, line 10 ---	
X	US 5 023 235 A (N GUYEN QUANG L ET AL) 11 June 1991 (1991-06-11)	1-3,10, 11, 16-18, 25,26 28
A	column 1, line 60 -column 2, line 35 --- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

14 November 2000

Date of mailing of the international search report

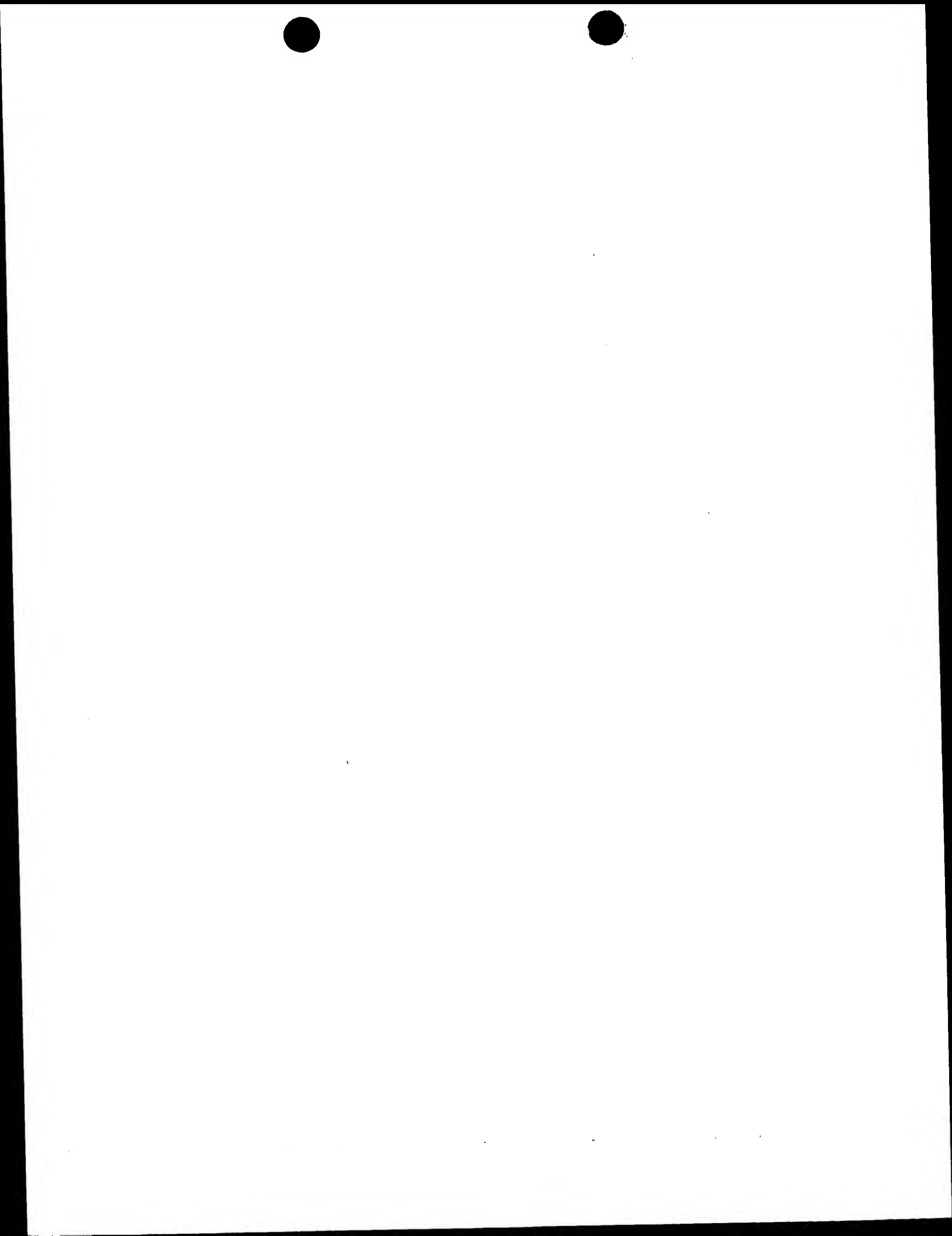
01/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

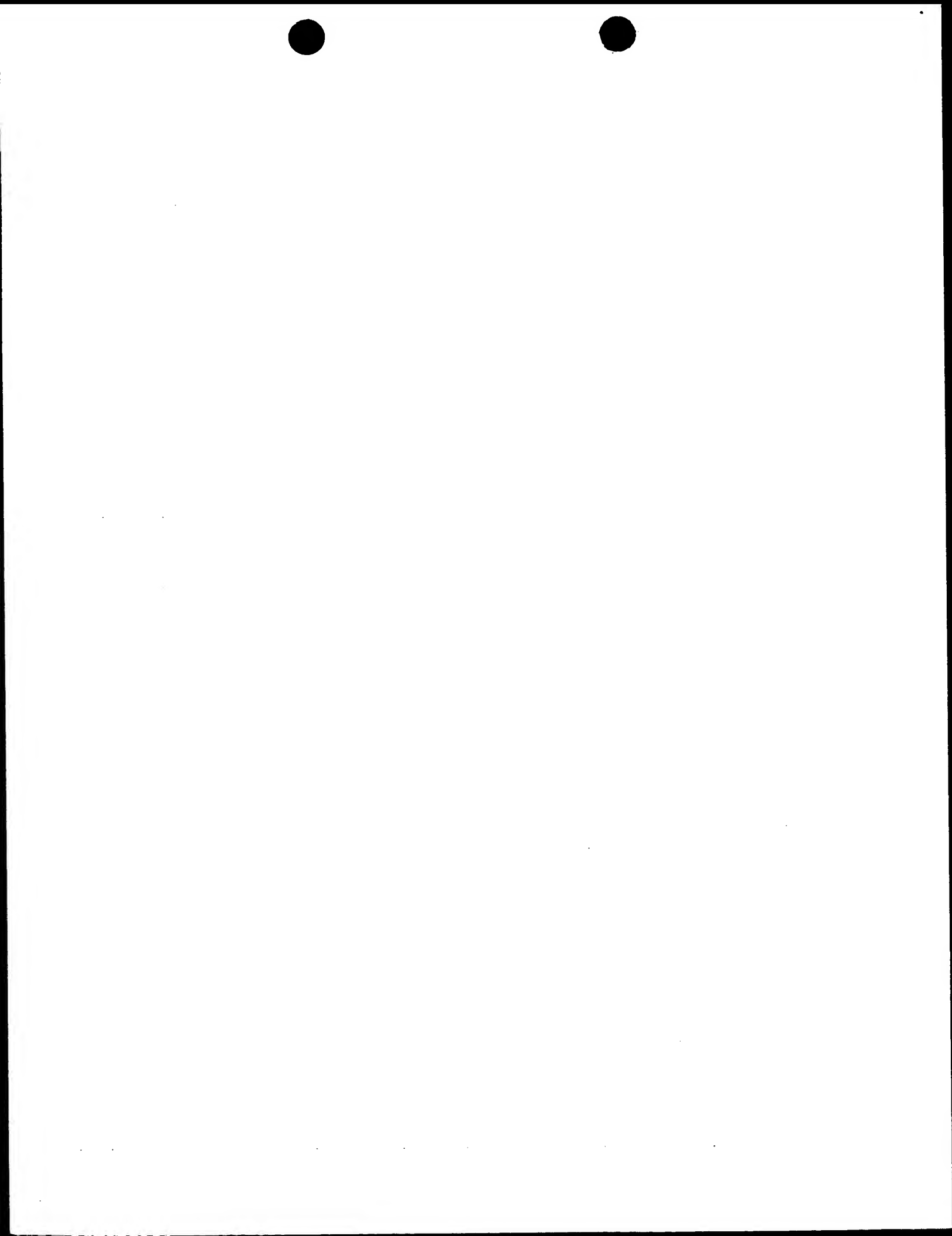
Authorized officer

Shade, M

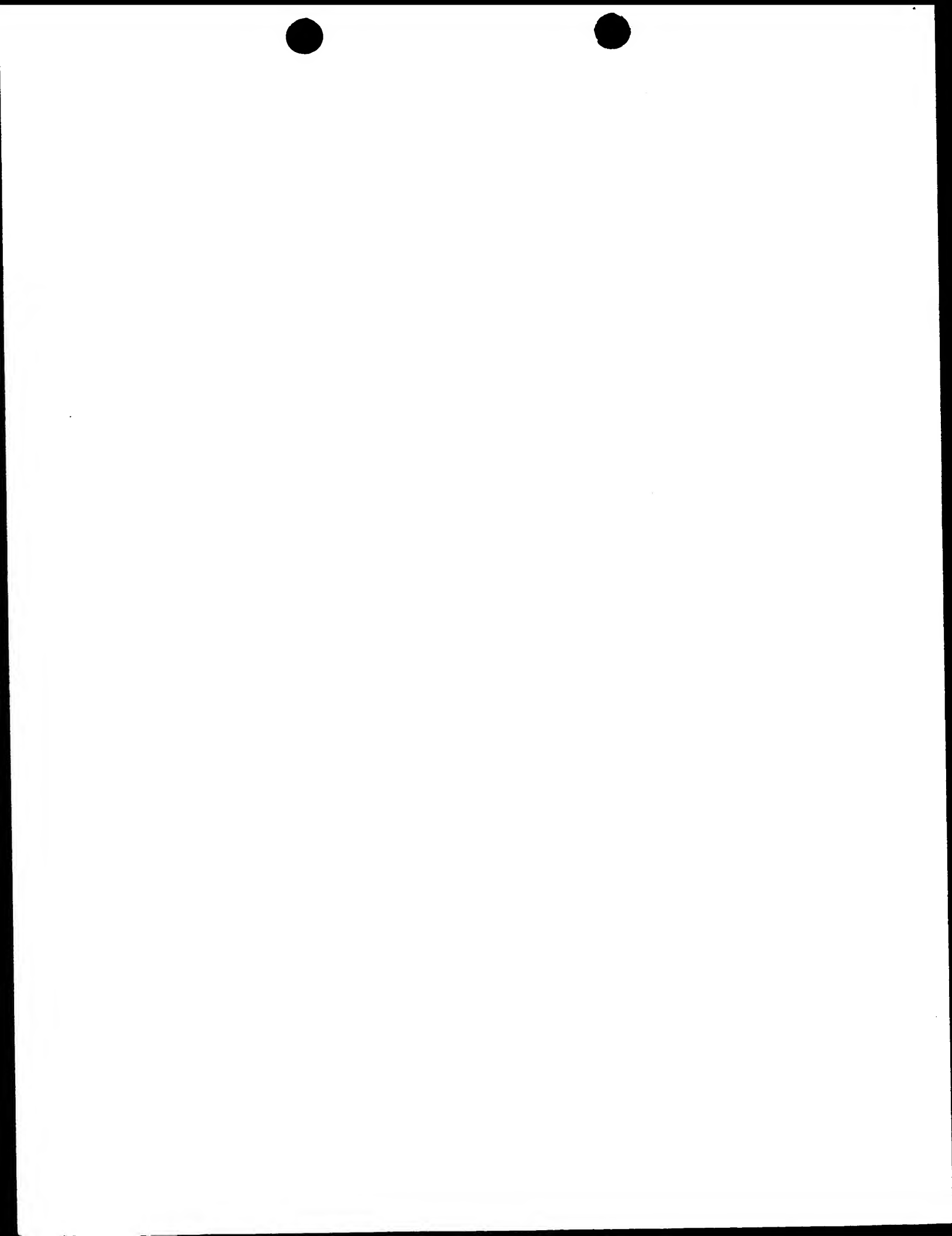


C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WINKLER, BARRY S.: "Unequivocal evidence in support of the nonenzymic redox coupling between glutathione/glutathione disulfide and ascorbic acid/dehydroascorbic acid" BIOCHIM. BIOPHYS. ACTA (1992), 1117(3), 287-90 , XP002152766 cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 288, column 1 -column 2 ---	28
Y	WO 99 07362 A (COSMETICOS NATURAL IND COM) 18 February 1999 (1999-02-18) cited in the application	1-3,5,6, 10,11, 16-18, 20,21, 25,26
A	page 11, line 5 -page 16, line 2 ---	28
A	US 5 140 043 A (PINNELL SHELDON R ET AL) 18 August 1992 (1992-08-18) column 3, line 18 -column 4, line 6 ---	1,16,28
A	WO 96 07396 A (JOHNSON & JOHNSON CONSUMER ;JOHNSON & JOHNSON MEDICAL K K (JP); LI) 14 March 1996 (1996-03-14) examples 1,12 ---	1,16,28
A	DATABASE WPI Section Ch, Week 199525 Derwent Publications Ltd., London, GB; Class B05, AN 1995-190139 XP002152767 & JP 07 107938 A (SANEIGEN FFI KK), 25 April 1995 (1995-04-25) abstract -----	28



Patent document cited in search report			Publication date		Patent family member(s)		Publication date	
US 5846996	A	08-12-1998	US	5945447	A		31-08-1999	
US 5023235	A	11-06-1991	FR	2610626	A		12-08-1988	
			DE	3870001	A		21-05-1992	
			DE	280606	T		11-05-1989	
			EP	0280606	A		31-08-1988	
			JP	63225689	A		20-09-1988	
WO 9907362	A	18-02-1999	BR	9704418	A		30-03-1999	
			BR	9704728	A		06-06-2000	
			EP	0949919	A		20-10-1999	
			US	6037481	A		14-03-2000	
US 5140043	A	18-08-1992	AT	156355	T		15-08-1997	
			AU	647699	B		24-03-1994	
			AU	5523990	A		16-11-1990	
			CA	2054189	A		18-10-1990	
			DE	69031219	D		11-09-1997	
			DE	69031219	T		22-01-1998	
			DK	486499	T		16-03-1998	
			EP	0486499	A		27-05-1992	
			ES	2104605	T		16-10-1997	
			HK	1001834	A		10-07-1998	
			JP	4507089	T		10-12-1992	
			WO	9012572	A		01-11-1990	
WO 9607396	A	14-03-1996	AU	3633295	A		27-03-1996	
			JP	8193019	A		30-07-1996	
			US	6080393	A		27-06-2000	
JP 7107938	A	25-04-1995	NONE					



[illegible]

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

IMPORTANT NOTIFICATION

Priority date (day/month/year)
16/07/1999

INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

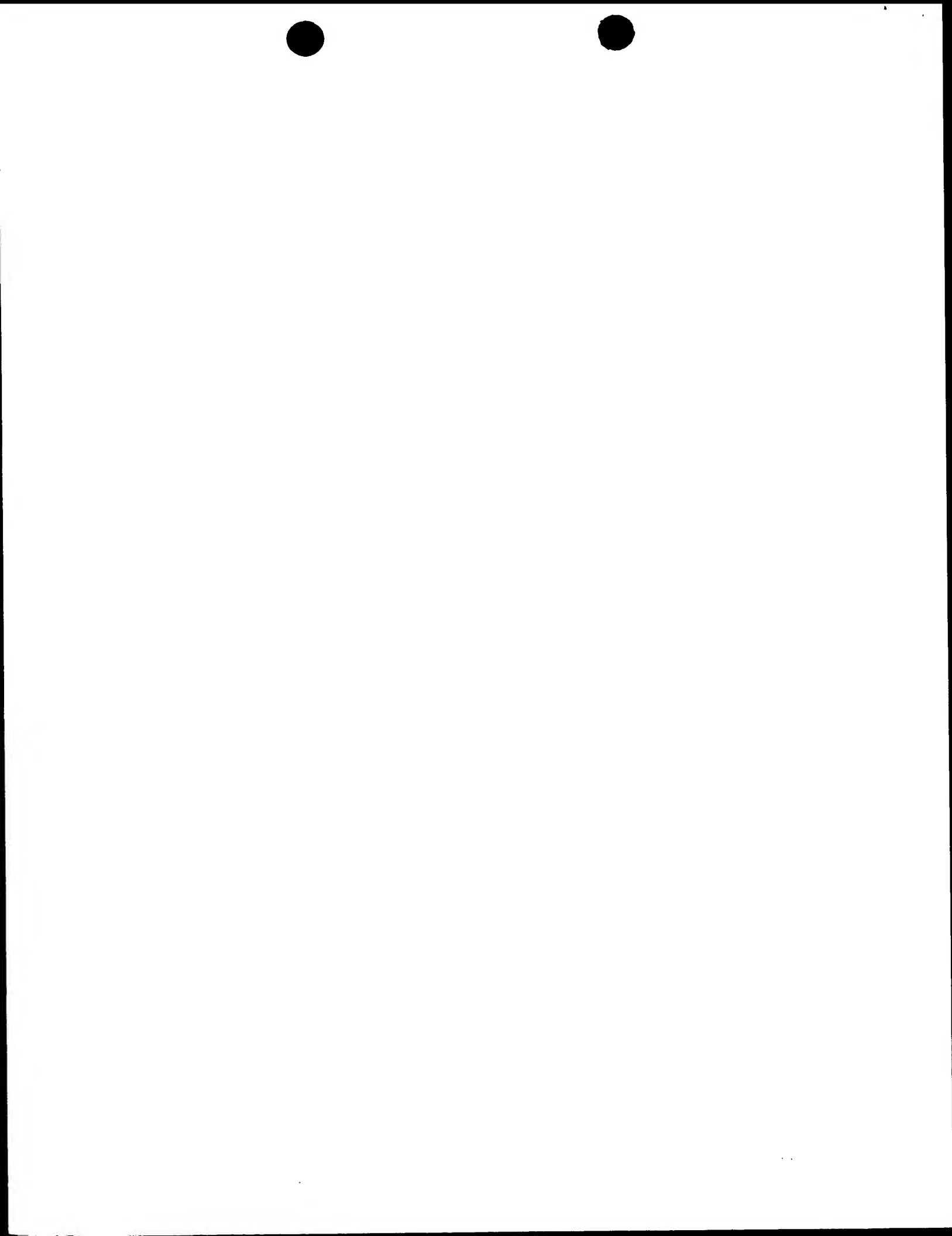
Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Authorized officer

Götz, K
Tel.+49 89 2399-7381





PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PE-3929	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/BR00/00078	International filing date (day/month/year) 14/07/2000	Priority date (day/month/year) 16/07/1999
International Patent Classification (IPC) or national classification and IPC A61K7/48		
Applicant INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
 - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 18 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 15/02/2001	Date of completion of this report 19.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pregetter, M Telephone No. +49 89 2399 8719 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BR00/00078

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-12 as received on 14/09/2001 with letter of 14/09/2001

Claims, No.:

1-45 as received on 14/09/2001 with letter of 14/09/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BR00/00078

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

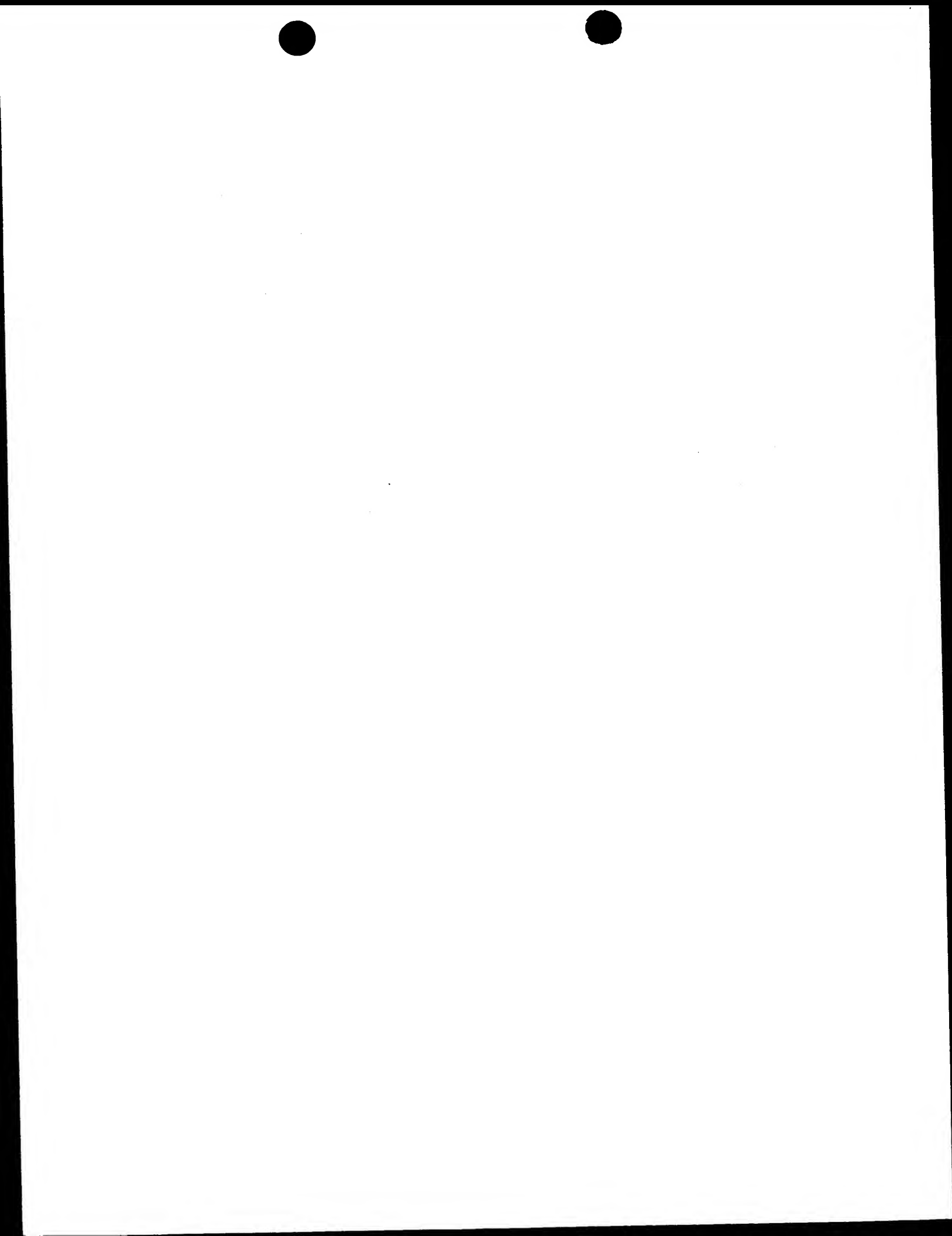
1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-45
Inventive step (IS)	Yes: Claims	
	No: Claims	1-45
Industrial applicability (IA)	Yes: Claims	1-45
	No: Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: US-A-5 804 168 (MURAD HOWARD) 8 September 1998 (1998-09-08)

D2: WO 99 33439 A (ROBERTS RICHARD L ;GREENE JAMES A (US);
SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08)

D3: US-A-5 902 591 (HERSTEIN MORRIS) 11 May 1999 (1999-05-11)

2. The subject-matter of present claim 1 is not novel according to Article 33(2) PCT. A process of contacting several compounds in aqueous medium necessarily takes place, when said compounds are all contained in the same aqueous solution/dispersion. Consequently, the same argumentation as given under point 3 applies.
3. The subject-matter of present claim 16 is not novel according to Article 33(2) PCT. D2 describes an oil-in-water formulation comprising an antioxidant compound in the aqueous phase (magnesium ascorbyl phosphate), a deoxygenating compound/oxygen removing compound (the most common humectants are glycols, which are given as examples of deoxygenating compounds), a metallic ions sequestering agent, a reducing agent (superoxide dismutase), and, in the dispersed phase, immunomodulator (beta glucan) and moisturizers/emollients (e.g. example 6). D3 discloses a mixture of 5% powdered ascorbic acid with 95% of an emulsion resulting in dissolving the ascorbic acid in the aqueous phase of said emulsion. The resulting aqueous phase comprises the ascorbic acid (antioxidant), a deoxygenating agent (butylene glycol), a metallic ions sequestering compound (EDTA) and a reducing agent (superoxide dismutase).
4. The subject-matter of present claim 28 is not novel according to Article 33(2) PCT. D2 describes an oil-in-water formulation comprising an antioxidant compound in the aqueous phase (magnesium ascorbyl phosphate), a deoxygenating compound (the most common humectants are glycols), a metallic ions



sequestering agent and a reducing agent (superoxide dismutase), and, in the dispersed phase moisturizers/emollients (hydrating comp.). Proanthocyanidins in the form of grape seed extract are also present (e.g. example 6).

5. With regard to the dependent claims, it is noted that a positive opinion can only be given, if dependent claims refer to independent claims that meet the requirements of the PCT.

Furthermore, the following has to be noted:

The use of a substance in certain percentages can only be considered to involve an inventive step, if it can be clearly shown that said percentages are unusual in the art and lead to a surprising effect.

The use of a specific immunomodulator, reducing agent, sequestering agent, ... can only be considered to involve an inventive step, if such a use is unusual in the art and leads to a surprising effect. However, the combination of specific compounds in specific percentages is very often not suggested by the prior art.

Re Item VIII

Certain observations on the international application

1. The subject-matter of claims 1, 16 and 28 is defined by using the term "comprise". This term "comprise" does not exclude the presence of further compounds.
2. Claim 38 defines glycerin as the hydration compound. The compound agent, according to claim 28 is in the "second phase". It is not clear, why glycerin should be present in the "second phase" and remain there, when chemically similar compounds, such as propylene glycol, are in the "first phase" (aqueous).

**Title: "A PROCESS FOR STABILIZING ANTIOXIDANT COMPOUNDS, AND
AQUEOUS COMPOSITIONS"**

Field of the Invention

5 The present invention relates to an improved process for stabilizing antioxidant compounds useful in cosmetic and pharmaceutical compositions.

Background of the Invention

10 An antioxidant compound is any compound or mixture of compounds that, when in contact with the skin, is capable of protect the skin against the action of free radicals.

15 Antioxidant compounds such as levogyrous ascorbic acid (LAA), popularly known as "Vitamin C", and proantocianidines (OPC) are widely used in the pharmaceutical and cosmetic industry since, among other characteristics, they act against the free radicals that speed up the aging process and degeneration of the cells.

20 One of the greatest technical difficulties for the use of the above antioxidant compounds is their instability. The LAA, for example, can easily be oxidized in the presence of atmospheric air, metallic ions or water, thus being transformed into dehydroascorbic acid, in addition to other by-products resulting from the oxidation. Such transformation diminishes its physiological properties, mainly under use conditions where the compound is exposed to the atmospheric air, metallic ions and water such as, for example, when incorporated into a topic solution.

25 In a simplified way, the instability of an antioxidant is expressed as a decrease of its reducing ability before it is contacted with the skin. In the case of the LAA, its instability is expressed as a compound degradation reaction.

 In the case of the OPC's the instability occurs through an oligomerization reaction, followed by polymerization.

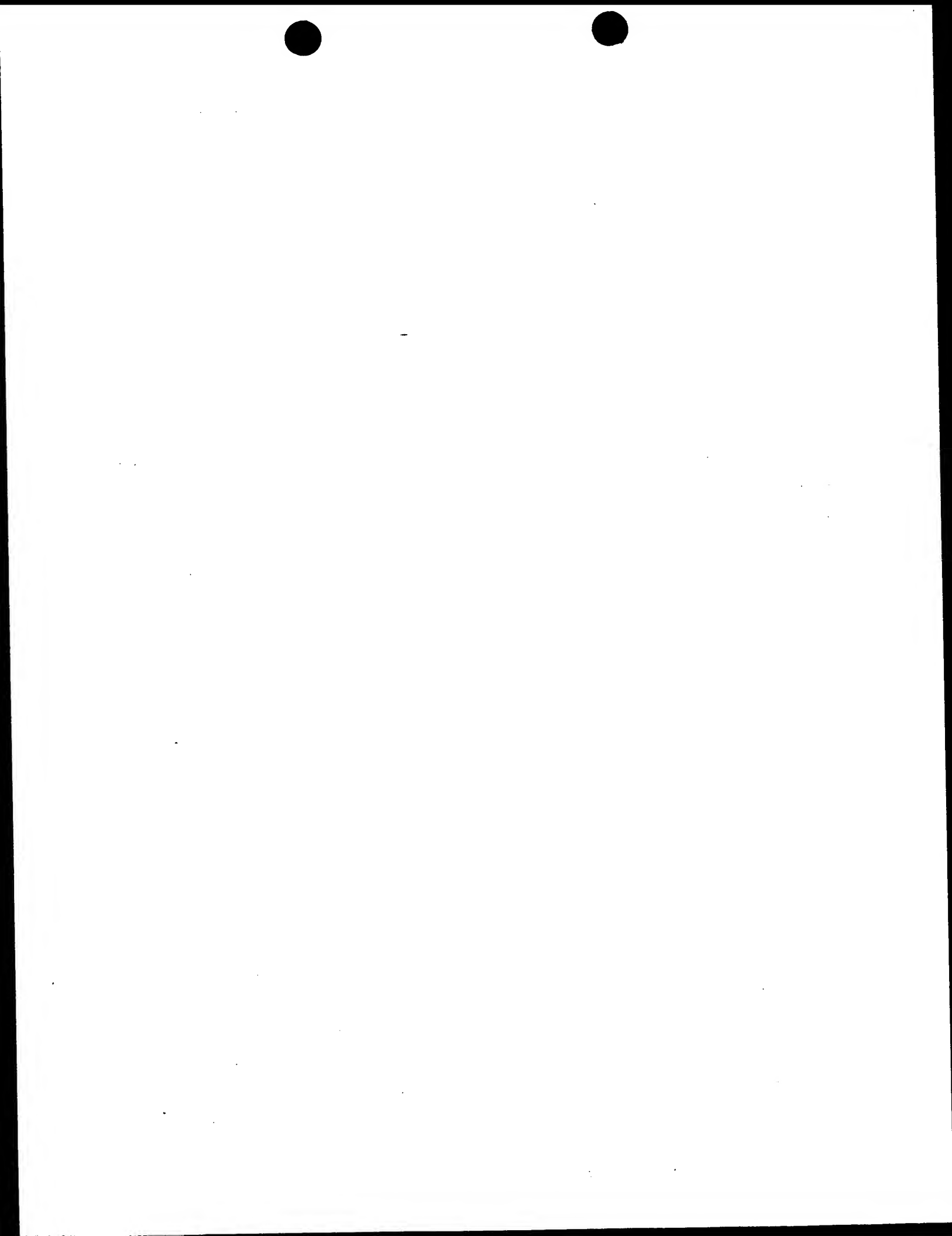
30 The LAA is often used in the form of its salts or esters due to this instability. The compositions prepared in this way attain stability for long periods of time.

Many studies have been carried out in order to obtain an aqueous composition containing stable antioxidant compounds. Some alternatives to stabilize LAA are described in Brazilian Patent Applications PI 9704418-0 and PI 9704728-7, filed by the same applicant of the present application. In said patent applications, processes for stabilizing levogyrous ascorbic acid (LAA) in a water-containing mean are disclosed comprising the step of contacting the LAA with at least one compound capable of forming hydrogen bridges with the LAA.

Another procedure known from the art for stabilizing antioxidants involves the association thereof with the compounds capable of reverting the decomposition reaction, the so-called "reducing agents". Once again, considering the LAA, for example, said compounds revert the dehydroascorbic acid formation reaction. However, the stabilization through this process results in compositions unacceptable for cosmetic use and many times unsuitable for medicinal use, since the required stoichiometric amount of reducing agents within the stoichiometry limits of the reaction must be too high so that the desired results could be attained. Since the reducing agents are usually selected from sulfur-containing compounds, the high content thereof in the resultant compositions bring about an unpleasant odor and sometimes their use are even legally forbidden. For example, in a solution containing a concentration of 5% by weight of LAA, which is a concentration range generally used in cosmetic-pharmaceutical products, contents of approximately 20% by weight of reducing agent should be required to ensure the LAA stability.

Another prior art reference that can be cited and that teaches the use of reducing agents, is a work published by Wrinkler, B.S. (Biochim, Biophy, Acta, 1117, 1992, pages 287 through 290), in which a compound is described (Glutathion) that can act as a reducer or reducing agent of dehydroascorbic acid by transforming same into ascorbic acid in the stoichiometric form. Through this work it was discovered that it was impossible to keep stoichiometric amounts of the components to produce a cosmetic composition since the Glutathion has an unpleasant odor which is a characteristic of sulphidric compounds.

Therefore, it is an object of the present invention to provide a process for stabilizing antioxidant compounds, that is, anti-free radicals or "anti-radicals", that makes it possible to overcome the drawbacks common to the known processes,



among which the ones that use the so-called reducing agents and, in a special way, that can result in stable, cosmetically more pleasant and more efficient compositions, also suitable for pharmaceutical use.

Summary of the Invention

5 The present invention is directed to a process for stabilizing antioxidant compounds comprising the step of adding to said compound, in an aqueous medium, at least one oxygen-removing compound, at least one metallic ion sequestering compound and at least one reducing agent.

10 The invention is also directed to compositions containing antioxidant compounds stabilized according to the above process.

Brief Description of the Drawings

 Figure 1 shows a stability graph of compositions containing LAA according to formulas prepared in accordance with the invention during at least 90 days at room temperature.

15 Figure 2 shows the stability graph of compositions containing OPC that is an oligomer of grape seed, with which it is possible to measure the stability of said OPC.

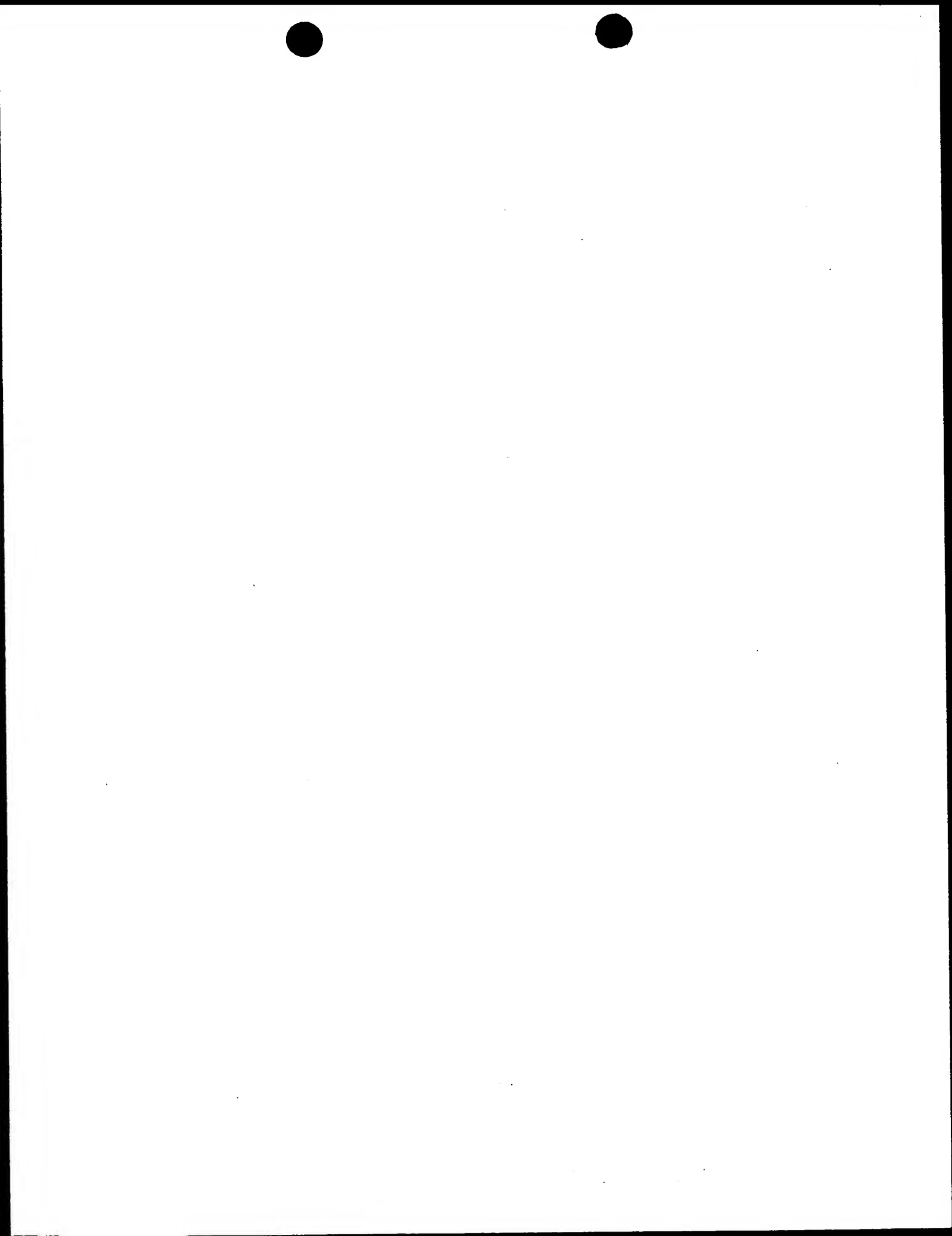
Detailed Description of the Invention

20 The present inventors have now found out that the association of at least one antioxidant compound with an reducing agent, in a aqueous medium, even without fulfilling the stoichiometry limits of the oxidation reaction, together with an oxygen-removing compound and a metallic ion sequestering agent, makes it possible to stabilize said antioxidant compound.

25 For the purposes of the present invention, some definitions of the terms used herein are given below.

 A reducing agent is to be understood as any compound or mixture of compounds having a higher oxidation potential than the oxidation potential of the oxidant to be stabilized so that the concentration of antioxidant sub-compounds to be generated turns back to the original antioxidant in its molecular form.

30 As to the oxygen-removing compound, or simply oxygen remover, is any compound or mixture of compounds capable of decreasing the oxygen solubility in a medium containing water and the antioxidant to be stabilized.



The metallic ion sequestering, or simply sequestering agent, is any compound or mixture of compounds having a high complexing constant and being effective for capturing and retaining such ions at pH values lower than 5.0. The effectiveness of the sequestering agent is defined by its ability to complexing the metallic ions present in a medium containing water and the antioxidant to be stabilized, so that it can minimize and preferably prevents the decomposition catalysis of any antioxidant present in said medium.

The invention is particularly suitable for providing the stabilization of compositions containing antioxidant compounds such as levogyrous ascorbic acid (LAA), or proantocianidines (OPC), or both, the resultant stability being effective for long periods of time.

In a first embodiment of the invention which is related to the stabilization of LAA in a aqueous medium, the oxygen-removing compound is selected from the group consisting of glycols, more preferably among propylene glycol and butylene glycol as well as mixtures thereof, even more preferably the propylene glycol.

The metallic ion sequestering compound, on its turn, is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates including di-, tri-, tetra- and pentavalent acids, the salts and mixtures thereof. More specifically the compound capable of sequestering metallic ions can be selected from the group consisting of sodium salt of 1-hydroxyethylidene (1,1-diphosphonic) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra(methylenephosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta(methylene phosphonic) acid, 1-hydroxyethylidene (1,1-diphosphonic) acid, and mixtures thereof. Preferably, 1-hydroxyethylidene (1,1-diphosphonic) acid is used as the metallic ion sequestering agent, which is commercialized under the name Dequest 2010 supplied by MONSANTO.

In accordance with a preferred embodiment of the invention, the process for stabilizing antioxidant compounds comprises a first step wherein an aqueous solution containing the oxygen-removing compound and the metallic ion sequestering agent at a ratio ranging from 2500:1 to 50:1 is prepared. In a second

step, the antioxidant compound is then added to the resultant solution in a aqueous medium.

In a third step, a LAA reducing agent is incorporated in the solution prepared in the first step described above, at a ratio ranging from 2520:1 to 20:1 related to the total mass of the oxygen-removing compound plus the sequestering agent mass, and at a ratio ranging from 1:0.02 to 3000:1, relating to the mass of the oxidizing compound. The great advantage achieved by the present invention is the notable stability of the LAA as time goes by. Compared to the compositions already known of the prior art containing this type of reducing agent, the invention allows the use of reducing agent in significantly low amounts, thus making it possible to use same for cosmetic and/or pharmaceutical compositions, thus advantageously overcoming the aspect of unpleasant odor and the legal limitations concerning the concentration of reducing agent.

Suitable reducing agent are those conventionally known for that purpose and include sulfur-containing compounds, preferably those selected from the group consisting of sodium dithionite, bisodium bisulfites, calcium bisulfites, potassium bisulfites and still more preferably Glutathion, as well as mixtures thereof.

Usually, for obtaining a commercially suitable cosmetic composition containing, for example, LAA as the antioxidant agent, the latter is used in a range from about 0.01% to about 30% and preferably from about 0.5% to about 20%, by weight, while the oxygen-removing compound is used in a range from about 10% to about 25%, preferably from about 16% to about 19%, and the sequestering agent is used in a range from about 0.01% to about 0.20%, preferably from about 0.10% to about 0.20%, all the percentages being by weight, based on the total weight of the composition. The reducing agent is present at a concentration from about 0.01% to about 0.5%, preferably from about 0.05% to about 0.2%. However, the amounts of these components will depend on the end uses for the resultant composition and should not limit the scope of the invention.

Among the antioxidant compounds of high importance in the cosmetic and pharmaceutical industry, the OPC's can also be cited, and they are advantageously stabilized by the process of the present invention. Regarding those OPC's that can be stabilized by the process of the invention, a more preferred



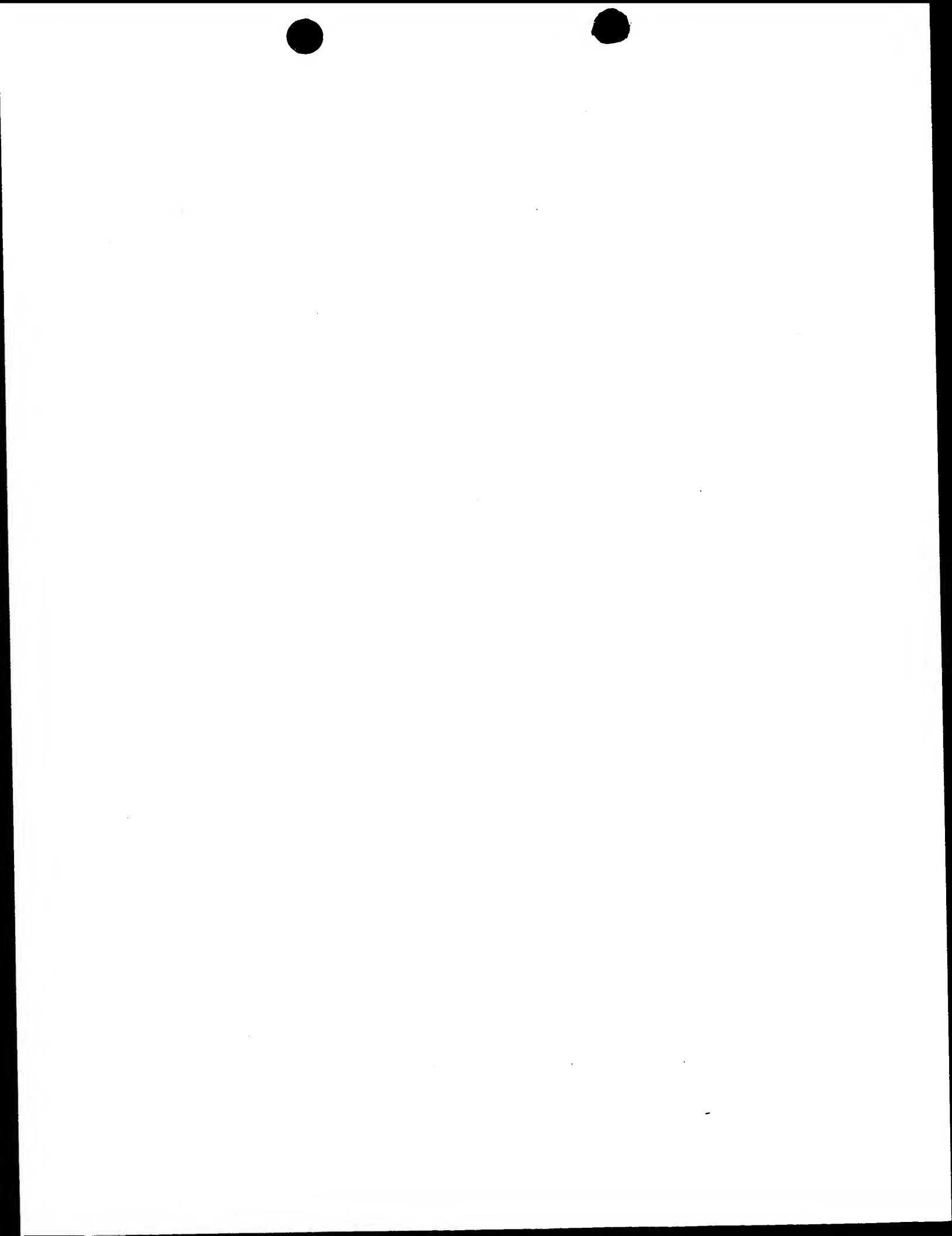
embodiment of the process comprises a first step of preparing a first composition comprising the oxygen-removing compound, the sequestering agent and the reducing agent, which is then added to the OPC contained in an aqueous medium. In this preferred embodiment, the first composition contains other antioxidant,
5 preferably the LAA.

Although the reasons are not yet fully defined, it was noticed that the presence of another antioxidant having characteristics similar to LAA in the first composition favors the stabilization of the OPC's. Without being too theoretical, it is believed that there is a synergy between the LAA present and the OPC's, resulting in
10 an advantageously stable composition.

In a particularly advantageous way, an aqueous composition containing the stabilized antioxidant in accordance with the present invention is used in a two-phase cosmetic composition. This kind of composition comprises, in a first phase, at least one antioxidant compound, an oxygen-removing compound, a metallic ion
15 sequestering compound and a reducing agent and, in a second phase, at least one hydrating compound. Preferably, the first and second phases are used at a weight ratio between them from 12:8 to 20:11, preferably of 16:9.

The two-phase composition described above has proved to be particularly suitable for regions where the skin is more delicate and, consequently, where it requires special care. "More delicate skin" must be understood as the one
20 more sensitive to the use of formulations that contain antioxidant compounds, emulsifying systems, fragrances, preservatives, cosmetic agents, among others. In the case of some antioxidant compounds, the use of high concentrations and the nature of these compounds can cause a higher exfoliation and irritation to the user
25 skin and a discomfort sensation.

For example, the delicate region around the eyes as well as other areas of the body require special care since the skin is thinner and fragile. The skin structure in this region is different: the epidermis and dermis are thinner, thus being more susceptible to the external aggressions and facilitating to the appearance of
30 wrinkles and expression marks. Collagen and elastin, that contribute to a higher skin stiffness and elasticity are also present in a lower amounts that helps to characterize the delicacy of the region.



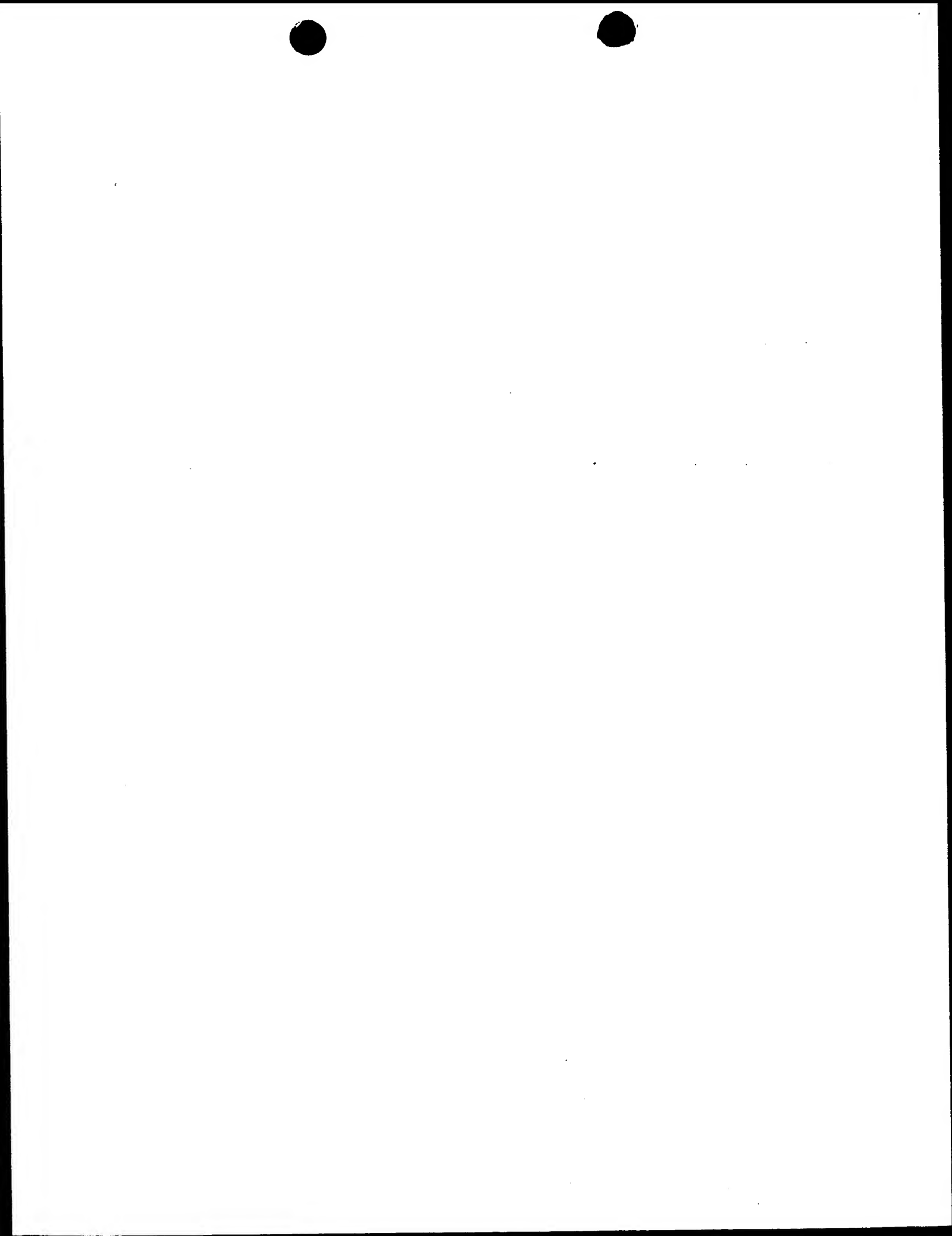
Hydrating agents as herein defined and useful for the present invention are those compounds or mixtures of compounds capable of increasing the water retention and restructuring the skin barrier for preventing the loss of water.

In a preferred way to formulate said two-phase composition, its first phase comprises an aqueous composition comprising an amount of 0.2 10%, preferably from 0.5 and 2%, of acid ascorbic and about 0.001 to 2.2%, preferably from 0.01 to 1.0%, of OPC's, particularly OPC from grape seed, and in its second phase a mixture of hydrating agents such as glycerin present at a concentration of 1.0 to 10% and 0.5 to 3.0% of ceramides contained in a liquid crystal emulsion, also called lamellar ceramide.

The lamellar ceramides help to restore the skin protection barrier, thus reinforcing the skin structure and consequently preventing the excessive loss of water. Together with glycerin, which is a soft hydrating agent and that increases the retention of water by the skin, it improves the hydration and softness thereof. The high glycerin concentration also provides a high hydration potential.

In as still more preferred way, the two-phase composition containing antioxidants stabilized in accordance with the invention is in the form of a homogeneous emulsion comprising an emulsifying system including at least two emulsifiers, one of which is selected from the group consisting of organosilicones of the copolyol family, preferably cetyl dimethicone copolyol, and a second one the molecular structure of which is similar to the natural skin lipids, preferably selected from a lipophylic stearic acid derived from a polyglycerol, more preferably polyglycerol-4-isostearate. The emulsifying system is advantageously added at a concentration of 0.5 to 8% by weight, based on the total weight of the composition.

In this emulsion form, the antioxidants together with the emulsifying system form micro-particles the size of which provides the emulsion with a better effectiveness and homogeneity. Since they are protected in micro-particles, the antioxidants, especially when it is OPC of grape seed, act on the walls of the blood vessels reinforcing same, what contributes to reduce the appearance of dark rings under the eyes and avoid the formation of such dark rings. Preferably, the emulsion particles are smaller than 3 μm , more preferably smaller than 2 μm , and still more preferably smaller than 1 μm .



The cosmetic composition as herein described may also comprise in its second phase from 13 to 25%, preferably from about 16 to 22% of emollients, from about 1 to 4% of an anti-radical agent, more preferably from 1.5 to 3.5% of Vitamin E, from about 0.001 to 0.3% of a preservative, more preferably 0.01 to 0.3% of sodium benzoate, and from about 0.05 to 0.6% of a thickening agent, more preferably from about 0.15 to 0.4% of colloidal silicon dioxide.

It was observed that the selection of the preservative agent is an important factor for the stabilization of the emulsion micro-particles due to its stripping ratio between the water and oil phases.

The illustrative examples and tests given below will better describe the present invention. However, the illustrated data and procedures merely refer to some embodiments of the present invention and should not be understood as limiting the scope of the invention.

Example 1

Comparative tests carried out by the inventors confirm the important paper of the reducing agent in the stabilization of antioxidants as per information obtained by Wrinkler B. S. in his work cited herein. A first test was carried out in order to determine the degradation kinetics of a 10% LAA solution in water-containing medium (m/v) under ultraviolet radiation, using a ultraviolet spectrophotometer, for 60 minutes. An immediate degradation of the LAA was observed, wherein a concentration of molecular LAA of about 9.58% (m/v) remained.

A stoichiometric amount of the reducing agent of the oxidation reaction, that is, Glutathion, was added to the previous post-irradiated solution. The resultant solution was irradiated with ultraviolet radiation for further 60 minutes. By analyzing the remaining LAA, it could be noticed that 9.50% (m/v) thereof was still present. Therefore, the degradation of the LAA is dramatically minimized after the reducing agent is added.

In a third test, a 10% LAA solution was prepared in a water-containing medium (m/v) with a stoichiometric amount of the reducing agent Glutathion. The solution was irradiated with ultraviolet radiation for 60 minutes. By analyzing the remaining LAA, a high content of 9.98% (m/v) was attained, thus confirming that the reducing agent inhibits the degradation of LAA. However, the use of said compound

in stoichiometric amounts still presents the already mentioned disadvantages.

For the purpose of evaluating the invention, stability tests of the antioxidants LAA and LAA associated with OPC's in a water-containing medium have been carried out. Twelve different formulas were prepared in accordance with the invention, the chemical compositions of which as well as the obtained results are discussed in the following Tables I and II.

Table I

Formula	Glutathion (% m/v) reducing agent	OPC (% m/v) Antioxidant	LAA (% m/v) Antioxidant	Remaining LAA (% m/v)
1	0.05	0	10	9.82
2	0.10	0	10	9.92
3	0.05	2	10	9.82
4	0.10	2	10	10.00

Table I shows the stability results of the LAA and OPC's measured by the respective remaining percentages; wherein formulas 1 through 4 have been prepared in accordance with the invention: formulas 1 and 2 including only LAA and formulas 3 and 4 comprising LAA associated with OPC's.

In the above tests, formulas 1 through 4 also comprise propylene glycol as an oxygen-removing compound, 2010 Dequest as the metallic ion sequestering agent and water.

It can be noticed from Table I that formulas 1 through 4 prepared in accordance with the invention show a LAA stability very close to 100% compared with the initial concentration.

Next, tests with further eight formulas have been carried out to evaluate the stability of LAA plus a gelling agent (Modified Xanthane Gum). Formulas 5, 8, 11 and 12 include sodium dithionite as an reducing agent, and formulas 6, 7, 9 and 10 use, again, Glutathion as the reducing agent, as shown in Table II

Table II

Formulas	Glutathion (% m/v) reducing agent	Sodium dithionite (% m/v) reducing agent	LAA (% m/v) Antioxidant	Remaining LAA (% m/v)
5	0.00	0.05	5.0	5.0
6	0.10	0.00	5.0	5.0
7	0.05	0.00	5.0	5.0
8	0.00	0.10	5.0	5.0
9	0.05	0.00	10.0	10.0
10	0.10	0.00	10.0	10.0
11	0.00	0.05	10.0	10.0
12	0.00	0.10	10.0	10.0

Table II shows the formulas evaluated as to stability of the LAA under ultraviolet radiation for 60 minutes. All the formulas contain propylene glycol, modified xanthane gum, Dequest 2010, PVA and water.

5 The purpose of the tests carried out with the compositions shown in Table II was to confirm that the stabilization of the LAA is successfully obtained with different reducing agents.

10 Sodium dithionite was used in formulas 5, 8, 11 and 12, resulting in a percentage of remaining LAA of about 100% after 90 days, which means that LAA practically does not undergo any degradation during at least 90 days at room temperature, maintaining the initial concentrations of its molecular form.

The reducing agent employed in formulas 6, 7, 9 and 10 is Glutathion. From Figure 1, it can be noticed that the percentage of remaining LAA in formulas 6 and 7 remains around 100% even in the presence of another reducing agent.

15 Figure 2 shows the stability graph of compositions containing OPC, which is a grape seed oligomer, through which it is possible to measure the stability of said OPC.

It can be noticed that the OPC's stability under the sun light is of at least 70% and around 80% in the dark, that latter being the normal condition for the final

commercial product, thus demonstrating that the result is favorable for the invention.

Example 2

A water-in-oil emulsion was prepared which comprises in a first phase:

Ingredient	% Mass	Function
Water	About 70	vehicle
Butylene glycol	1 to 4	Oxygen-removing compound
Glutathion	0.1	reducing agent
1-Hydroxyethylidene (1,1-diphosphonic) acid (Dequest ®)	0.15	Metallic ion sequestering agent
LAA	from 1 to 30	Antioxidant agent
Grape seed OPC	0.3	Antioxidant agent

and, in a second phase

Ingredient	% Mass	Function
Glycerin	7.0	Hydrating agent
Lamellar Ceramides	1.0	Hydrating agent
Cetyl dimethicone copolyol	2.0	Emulsifier
Triglycerol isostearate 4	2.0	Emulsifier
Vitamin E	2.0	Antioxidant
Sodium benzoate	0.3	Preservative
Colloidal silicon dioxide	0.3	Thickening agent
Magnesium sulphate	0.7	Thickening agent
Cyclomethicone D5/d6	13.5	Emollient
Isohexadecane	5.0	Solvent

5 A panel was composed in a blind study, with 80 female volunteers with ages ranging between 25 and 65 years, evaluated at two different times: after the fifteenth day of use (T15) and at the 30th day of use (T30). The product was supplied at ratios of about 16:9 of the first phase to the second phase and according to the composition described in the example above. The results of this evaluation
10 are given in table III where the expressed percentages refer to the percentage of

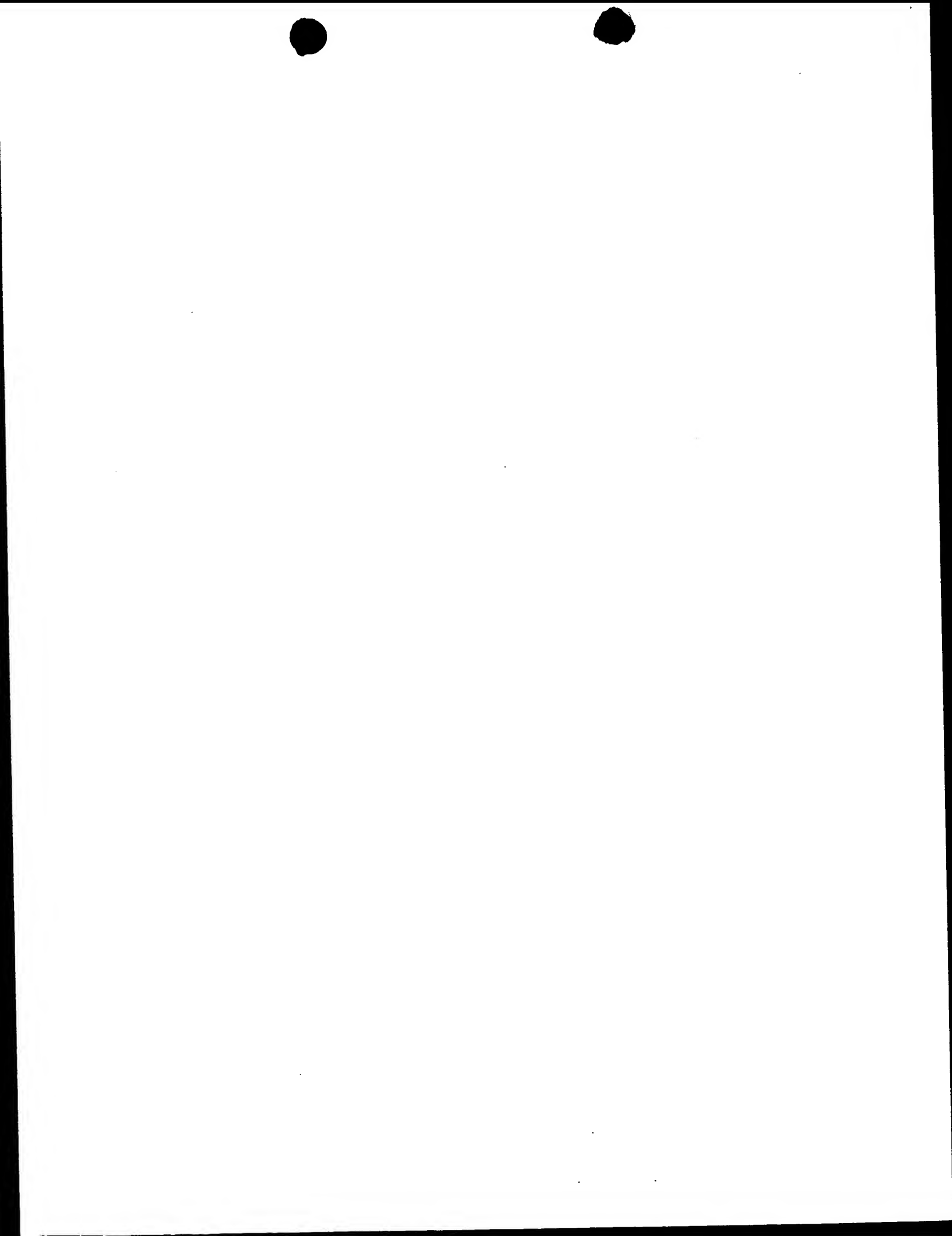
users that perceived the occurrence of the corresponding benefit.

Table III - Evaluation of the product performance by the physician

	T15	T30
Wrinkles	16.6%	31.2%
Flaccidity	8.7%	16.6%
Drying	11.2%	63.7%
Rings under the eyes	17.5%	27.5%
Edema	12.5%	22.5%

Amongst the product beneficial effects, including those evaluated the test, the following should be stressed out:

- 5
- it alleviated the skin aging marks around the eyes, such as wrinkles and flaccidity;
 - it reduced the dark rings and pockets under the eyes;
 - it improved the stiffness of the skin;



CLAIMS

1. A process for stabilizing antioxidant compounds characterized by comprising the step of contacting said compound, in an aqueous medium, with an oxygen-removing compound, a metallic ion sequestering compound and an reducing agent.

2. A process in accordance with claim 1, characterized in that the antioxidant compound is selected from group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's)

3. A process in accordance with any one of claims 1 and 2, characterized in that the antioxidant is LAA.

4. A process in accordance with any one of claims 1 to 3, characterized in that it further comprises a proantocianidine (OPC)

5. A process in accordance with any one of the previous claims characterized in that the oxygen-removing compound is a glycol.

6. A process in accordance with claim 5, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and mixtures thereof, more preferably propylene glycol.

7. A process in accordance with any one of the previous claims, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates that include di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

8. A process in accordance with claim 7, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxyethylidene (1,1-diphosphonic) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra (methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta (methylene phosphonic) acid, 1-hydroxyethylidene (1,1-diphosphonic) acid and the mixtures thereof.

9. A process in accordance with claim 8, characterized in that the metallic ion sequestering agent is 1-hydroxyethylidene (1,1-diphosphonic) acid.

10. A process in accordance with any one of the previous claims characterized in that the reducing agent is selected from the group consisting of sodium dithionite, sodium bisulfites, calcium bisulfites, potassium bisulfites and Glutathion, as well as the mixtures thereof.

5 11. A process in accordance with claim 10, characterized in that the reducing agent is Glutathion or sodium dithionite.

10 12. A process in accordance with any one of the previous claims, characterized by comprising a first step of preparing an aqueous solution containing the oxygen-removing compound, the metallic ion sequestering agent and the reducing agent, and a second stage of adding the antioxidant to the thus prepared composition, in a aqueous medium.

15 13. A process in accordance with claim 12, characterized in fact of the composition formed in the first step comprises the oxygen-removing compound in a range from about 10% to about 25%, the metallic ion sequestering agent in a range from about 0.01% to about 0.20%, the reducing agent at a concentration of about 0.01% to about 0.5%, the content of the antioxidant being from about 0.01% to about 30%, all the percentages being by weight based on the total weight of the composition.

20 14. A process in accordance with claim 13, characterized in fact of the composition formed in the first step comprises the oxygen-removing compound in a range from about 16% to about 19%, the metallic ion sequestering agent in a range from about 0.10% to about 0.20% and the reducing agent at a concentration from about 0.05% to about 0.2%, the content of the antioxidant being from about 0.5% to about 20% by weight.

25 15. A process in accordance with claim 12, characterized in that said antioxidant added in the second stage is an OPC and in that the first step also comprises the addition of LAA.

30 16. An aqueous composition comprising at least one antioxidant, characterized by further comprising an oxygen-removing compound, a metallic ion sequestering agent and a reducing agent.

17. An aqueous composition in accordance with claim 16, characterized in that the antioxidant is selected from the group consisting of levogyrous ascorbic

acid (LAA) and proantocianidines (OPC's)

18. An aqueous composition in accordance with any one of claims 16 and 17, characterized in that the antioxidant is LAA.

19. An aqueous composition in accordance with claims 16 the 17, characterized in that the antioxidant comprises proantocianidines (OPC's)

20. An aqueous composition in accordance with any one of claims 16 to 19, characterized in that the oxygen-removing compound is a glycol.

21. An aqueous composition in accordance with claim 20, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and mixtures thereof, more preferably propylene glycol.

22. An aqueous composition in accordance with any one of claims 16 to 21, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates including di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

23. An aqueous composition in accordance with claim 22, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxyethylidene (1,1-diphosphonic) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra (methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta (methylene phosphonic) acid, 1-hydroxyethylidene (1,1-diphosphonic) acid and mixtures thereof.

24. An aqueous composition in accordance with claim 23, characterized in that the metallic ion sequestering agent is 1-hydroxyethylidene (1,1-diphosphonic) acid.

25. An aqueous composition in accordance with any one of claims 16 to 24 characterized in that the reducing agent is selected from the group comprising sodium dithionite, sodium bissulfites, calcium bissulfites, potassium bissulfites and Glutathion, as well as mixtures thereof.

26. An aqueous composition in accordance with claim 25, characterized in that the reducing agent is Glutathion or sodium dithionite.

27. An aqueous composition in accordance with claim 18, characterized

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by comprising from about 0.01% to about 30% of LAA, from about 10% to about 25% of an oxygen-removing compound, from about 0.01% to about 0.20% of a metallic ion sequestering agent, and from about 0.01% to about 0.5% of a reducing agent.

28. A two-phase aqueous cosmetic composition, characterized by comprising, in a first phase, at least one antioxidant, an oxygen-removing compound, a metallic ion sequestering agent and a reducing agent and, in a second phase, at least one hydrating compound.

29. A two-phase composition in accordance with claim 28, characterized in that the weight ratio between the first and second phases is from about 12:8 to 20:11.

30. A two-phase composition in accordance with claim 28 or 29, characterized in that said at least one antioxidant is selected from the group consisting of levogyrous ascorbic acid (LAA) and proantocianidines (OPC's).

31. A two-phase composition in accordance with any one of claims 28 to 30 characterized in that the oxygen-removing compound is a glycol.

32. A two-phase composition in accordance with claim 31, characterized in that the oxygen-removing compound is selected from propylene glycol, butylene glycol and the mixtures thereof, more preferably propylene glycol.

33. A two-phase composition in accordance with any one of claims 28 to 32, characterized in that the metallic ion sequestering agent is selected from the group consisting of ethylene phosphonic acids, the salts and mixtures thereof, or from the group consisting of phosphonates that include di-, tri-, tetra- and pentavalent acids, their salts and mixtures thereof.

34. A two-phase composition in accordance with claim 33, characterized in that the metallic ion sequestering agent is selected from the group consisting of sodium salt of 1-hydroxyethylidene (1,1-diphosphonic) acid, ethylene diamine tetra(methylenephosphonic) acid, sodium salt of ethylene diamine tetra(methylene phosphonic) acid, diethylene diamine penta(methylenephosphonic) acid, sodium salt of diethylene diamine penta(methylene phosphonic) acid, 1-hydroxyethylidene (1,1-diphosphonic) acid and mixtures thereof.

35. A two-phase composition in accordance with claim 34, characterized in that the metallic ion sequestering agent is 1-hydroxyethylidene (1,1-diphosphonic)

acid.

36. A two-phase composition in accordance with any one of claims 28 to 35 characterized in that the reducing agent is selected from the group comprising sodium dithionite, sodium bissulfites, calcium bissulfites, potassium bissulfites and
5 Glutathion, as well as mixtures thereof.

37. An aqueous two-phase composition in accordance with claim 36, characterized in that the reducing agent is Glutathion or sodium dithionite.

38. A two-phase composition in accordance with any one of claims 28 the 37, characterized in that the hydrating compound is glycerin.

10 39. A two-phase composition in accordance with any one of claims 28 to 37, characterized in that the second phase comprises ceramides in a liquid crystal emulsion form.

40. A two-phase composition in accordance with claim 39, characterized by comprising, in the first phase, an aqueous composition comprising an amount of
15 0.2 to 10% of ascorbic acid and about 0.001 to 2.2% of OPC's and, in the second phase, glycerin in a range from 1.0 to 10%, and 0.5 to 3.0% of ceramides contained in a liquid crystal emulsion, all percentages being based on the total weight of the composition.

41. A two-phase composition in accordance with any one of claims 28 to
20 40, characterized by further comprising, in its second phase, about 13 to 25% of emollients, about 1 to 4% of an anti-radical agent, about 0.001 to 0.3% of a preservative, and about 0.05 to 0.6% of a thickening agent.

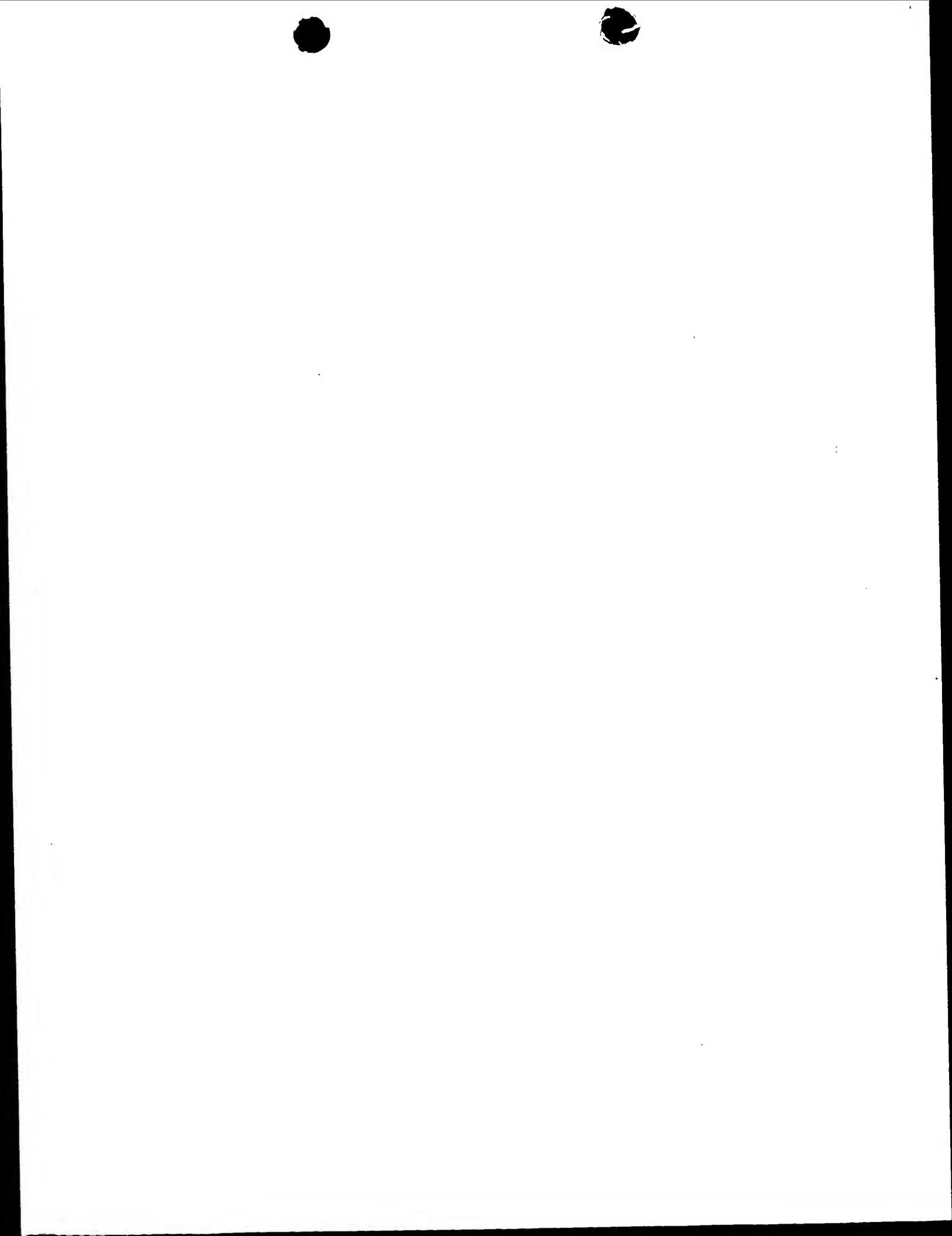
42. A composition in accordance with any one of claims 28 to 41, characterized by being in the form of an homogeneous emulsion containing an
25 emulsifying system comprising a first emulsifier selected from the group consisting of organosilicones and a second emulsifier having a molecular structure similar to that of skin lipids.

43. A composition in accordance with claim 42, characterized in that said organosilicone is cetyl dimethicone copolyol and the second emulsifier is
30 polyglycerol-4-isostearate.

44. A composition in accordance with claim 42 or 43, characterized by being in the form of micro-particles smaller than 3 μm .

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45. A composition in accordance with claim 44, characterized in that the micro-particles have a size smaller than 1 μm .

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